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SYNTHESIS OF ANTIMALARIAL AGENTS FROM  
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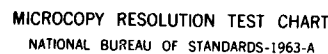
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REPORT NUMBER FIVE

SYNTHESIS OF ANTIMALARIAL AGENTS FROM  
2,3-DIHYDRO-1,6-DIAZAPHENALENE DERIVATIVES

Annual Summary Report

January 1, 1980 to December 31, 1980

JAMES M. COOK

March, 1982

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-78-C-8003

Department of Chemistry  
University of Wisconsin-Milwaukee  
Milwaukee, Wisconsin 53201

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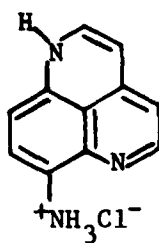
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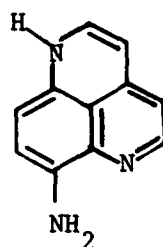
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In agreement with our original synthetic plan 7-nitro-2,5-dichloro-1,6-diazaphenalene (41) was converted in one step to 7-amino-1,6-diazaphenalene dihydrochloride (1); however conversion of this stable salt into the free base 2 resulted in decomposition of 2 prohibiting attachment of the alkylamino side chains to this molecule. Consequently, a variety of experiments were carried out on 1,6-diazaphenalene (4) to define the chemistry of this molecule. This included reaction of 4 with electrophiles ( $^+NO_2$ , $^+Br$ , $^+I$ , $^+Cl$ , $PhN_2^+$ ), acylating agents and alkylhalides. In addition, 4 was reacted with oxidizing agents such as singlet		

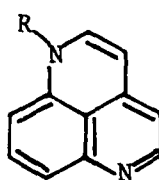
oxygen and peracids. It was found that 4 reacted with many of these agents in similar fashion to that previously reported for imidazole. Use of the LDA/alkyl-



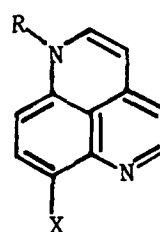
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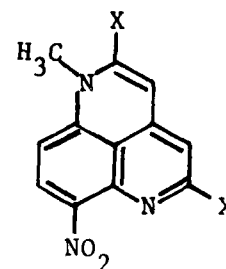
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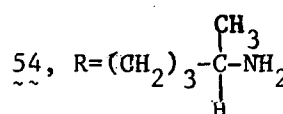
46, R=CH<sub>3</sub>



30, R=H, X=I



55, X=H or Cl



54, R=(CH<sub>2</sub>)<sub>3</sub>-C(CH<sub>3</sub>)<sub>2</sub>-NH<sub>2</sub>

50, R=CH<sub>3</sub>, X=Br

ation technology developed during this study resulted in the synthesis of the target 54, moreover, syntheses of other key compounds 30, 46, 50, and 55 have been accomplished. These bases should be more useful for preparation of anti-malarial agents for they provide entry into 1-alkyl-7-aminoalkyl-1,6-diazaphenyl-  
lenes which would appear to be much more stable than 2.

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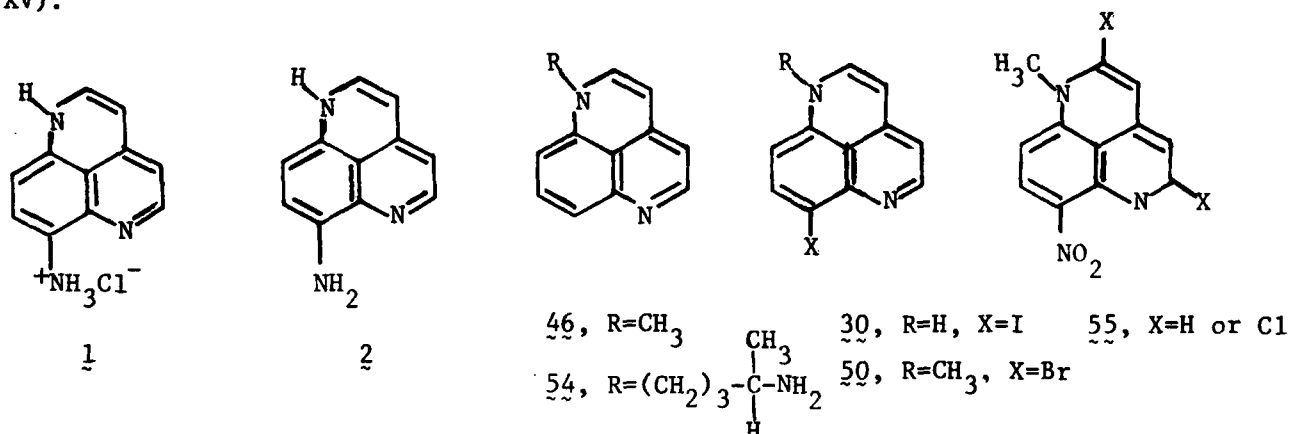
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# SUMMARY

In agreement with our original synthetic plan 7-nitro-2,5-dichloro-1,6-diazaphenalene (41) was converted in one step to 7-amino-1,6-diazaphenalene dihydrochloride (1). This salt was stable enough to characterize; however, treatment of 1 with base generated the amine 2 which immediately turned red-black, as illustrated in Scheme I. The lability of 2 interfered with all attempts to alkylate the molecule with alkyl halides or by reductive alkylation; consequently, this report concerns attempts to define the chemistry of 1,6-diazaphenalene (4) with the express purpose of preparing molecules similar to 2, such as 7, but which do not undergo oxidation as readily as 2 (see Scheme II). In addition, other routes to the target compounds were also explored.

It is known that p-N,N-dimethylaniline is less prone to oxidative decomposition than the corresponding p-aminoaniline; consequently, it was felt substitution of an alkyl group at position-1 of 4 would retard the oxidation of the 1-substituted-7-aminoderivative (see Schemes II and III) and permit alkylation with the necessary side chains. In this vein, 1,6-diazaphenalene (4) has been alkylated (LDA, HMPA, THF) with methyl iodide or benzyl bromide in very good yield to provide the N-alkylated derivatives 46 and 47, respectively. This technology has also provided the first entry into a target compound (see Structure 54, Scheme XV).



Theoretical calculations and experimental results both indicated that reaction of the protonated 16 form of 1,6-diazaphenalene with electrophiles [<sup>+</sup>NO, <sup>+</sup>Br, <sup>+</sup>I, and PhN<sup>+</sup>] would give the desired 7-substituted-1,6-diazaphenalene as the predominant product. This method has been employed to prepare both 7-bromo-1,6-diazaphenalene (20, 81% yield) and 7-iodo-1,6-diazaphenalene 30; two molecules which are suitably functionalized for copper catalyzed addition of an alkylamino group to position-7 of a diazaphenalene. Furthermore, the 7-bromo-diazaphenalene (20) has been converted in greater than 70% yield to 1-methyl-7-bromo-1,6-diazaphenalene 50, which permits a different entry into 1-alkyl-7-aminoalkyl-1,6-diazaphenalene targets listed under B.1. Along these same lines 1-methyl-7-nitro-1,6-diazaphenalene 55 has been synthesized which yields yet another route to 1-substituted-7-amino-1,6-diazaphenalenenes which should be more stable than 2. This remains, however, to be tested in practice.

The oxidation of 4 has been carried out with singlet oxygen, and also with peracids. The reaction with singlet oxygen to form the enone 32 is quite interesting for it parallels similar observations in the imidazole area, and also illustrates yet another route (see Scheme XVIII) to targets (9-methoxy series) outlined under B.1. Peracid oxidation of 4 gave enones 37 and 38; however, oxidation had also taken place at the 1,2 and 6-positions, in contrast to the results with singlet oxygen. Attempts to block the 1-position of 4 with acyl groups were generally unsuccessful because the N-acyldiazaphenalenenes were more labile than N-acylimidazoles, but one acyldiazaphenalene 44 was isolable, primarily due to its unique

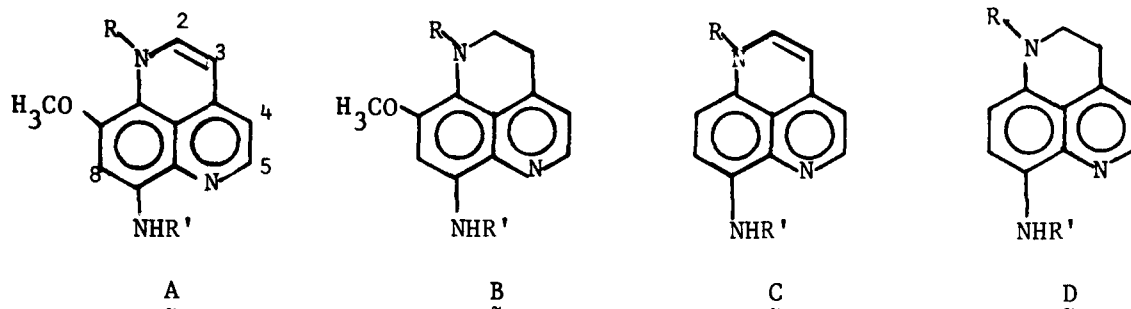
substitution pattern.

Finally, the behavior of 1,6-diazaphenalene toward electrophiles, acylating agents and singlet oxygen is similar to the behavior of imidazole under these conditions. Alkylation, however, does not occur as readily with 4; although, the use of LDA/HMPA now permits successful alkylations to be completed in better than 75% yield. Moreover, the facile synthesis of nitro, halo and 1-alkyl-diazaphenalenenes discussed in the following report should provide several different routes to the desired targets outlined under B.1.

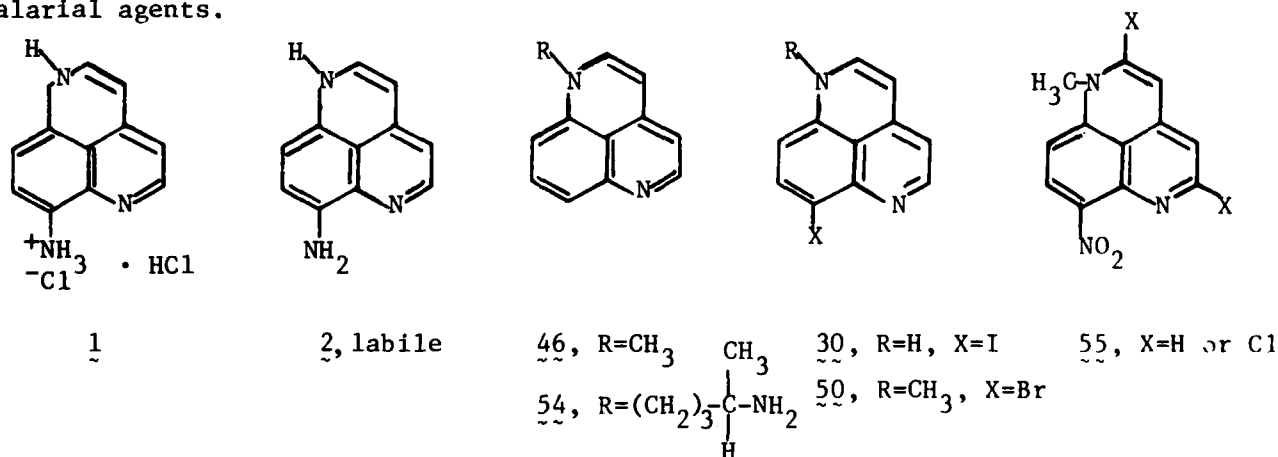


## FOREWORD

The following report concerns research directed toward the synthesis of potential antimalarial agents, based on the structures of 9-methoxy and 9-H-7-alkylamino-1,6-diazaphenalene bases (A, C) and their 2,3-dihydro analogs (B, D); the resemblance to 5,8-diaminoquinolines, however, is not accidental.



One of the key intermediates of this work, 7-amino-1,6-diazaphenalene dihydrochloride (1) was prepared over a year ago; however, conversion of this stable salt to the free base (2) resulted in decomposition of 2 prohibiting simple alkylation of the material; a necessary step to provide targets such as C. Consequently, a series of different experiments were carried out on 1,6-diazaphenalene (4) to define the chemistry of this base. This includes reaction of 4 with electrophiles [ $^+\text{NO}_2$ ,  $^+\text{Br}$ ,  $^+\text{I}$ ,  $^+\text{Cl}$ ,  $\text{PhN}_2^+$ ], acylating and alkylating agents. In addition, 4 was reacted with oxidizing agents such as peracids and singlet oxygen. It was found that 4 reacted with many of these agents in similar fashion to that previously reported for imidazole. Use of the alkylation technology developed during this study resulted in the synthesis of the target 54, moreover syntheses of other key compounds 30, 46, 50 and 55 have been completed. These bases should be more useful for preparation of stable 1-alkyl-7-aminoalkyl-1,6-diazaphenalenes which would appear more practical, in a chemical sense, for pursuit as potential antimalarial agents.



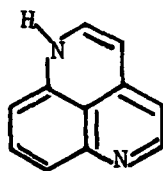
This report is not written in exact chronological order, however, we have adhered to this order of events in most cases. The reaction of 1,6-diazaphenalene 4 with electrophiles in both acidic and neutral media is presented followed by acylation and alkylation of this base. This is followed by synthesis of the target 54 using the LDA/alkylation technology. The oxidation of 4 with singlet oxygen or peracids is next discussed followed by comparison of the chemical properties of 4 to those reported for imidazole. Finally, a summary of potential routes to targets listed under B.1. is presented employing compounds such as 30, 46, 50, and 55, prepared in the last year. The very last portion of the report is a detailed experimental section.

## TABLE OF CONTENTS

	<u>Page</u>
FRONT COVER	i
ABSTRACT (DD Form 1473)	ii
TITLE PAGE	iv
SUMMARY	v
FORWORD	vii
TABLE OF CONTENTS	1
INTERMEDIATES SUBMITTED FOR SCREENING	2
WORK IN PROGRESS	2
Table I: Bromination of 1,6-Diazaphenalene	9
Table II: Reaction of 1,6-Diazaphenalene with N-Halosuccinimides	13
EXPERIMENTAL	27
Figure 1: Total electron densities for 1,6-diazaphen- alene <u>1</u> , the protonated form <u>2</u> , and the anion <u>3</u>	38
Figure 2: Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (IUMO) reactions of 1,6-diazaphenalene <u>1</u>	39
Figure 3: Calculated HOMO and LUMO densities for protonated 1,6-diazaphenalene <u>2</u>	40
Figure 4: Calculated HOMO and LUMO densities for the anion <u>3</u>	41
Figure 5: Calculated bond orders ( $\pi$ ) for 1,6-diaza- phenalene <u>1</u> , the cation <u>2</u> , and anion <u>3</u>	42
Figure 6: Total electron densities for 1,6-diazaphen- alene <u>1</u> , 3-chloro-1,6-diazaphenalene <u>10</u> , and 2,3-dichloro-1,6-diazaphenalene <u>11</u>	43
Figure 7: Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (IUMO) reactions on 3-chloro-1,6-diazaphen- alene <u>10</u>	44
Figure 8: Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (IUMO) reactions on 2,3-dichloro-1,6-diaza- phenalene <u>11</u>	45
Figure 9: Calculated bond orders ( $\pi$ ) for 1,6-diaza- phenalene <u>1</u> , 3-chloro-1,6-diazaphenalene <u>10</u> , and 2,3-dichloro-1,6-diazaphenalene <u>11</u>	46
Figure 10: Proton NMR of 1-methyl-7-Nitro-1,6-Diaza- phenalene and 7-Nitro-1,6-Diazaphenalene, Respectively	47
REFERENCES	48
DISTRIBUTION LIST	51

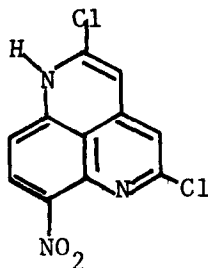
## A. Intermediates Submitted for Screening

1. Intermediates sent for screening whose structures have been unambiguously assigned.



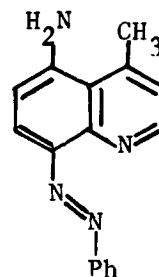
41 (500 mg)

BJ34090(6.0/6.1, toxic)



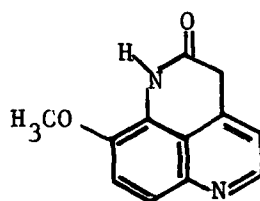
41 (500 mg)

BJ34081( $\frac{6.4}{6.1}$ )



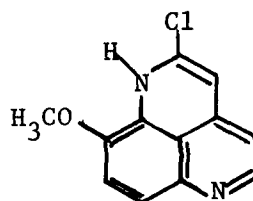
(500 mg)

BJ34063( $\frac{6.5}{6.1}$ , toxic)



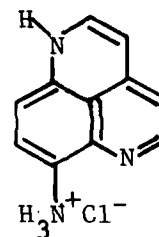
(500 mg)

BJ34296( $\frac{6.4}{6.1}$ )



(500 mg)

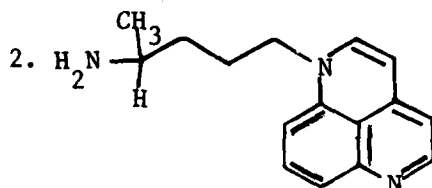
BJ34072( $\frac{6.4}{6.1}$ )



• HCl

1 (500 mg)

BJ59088(toxic)



• 2HCl

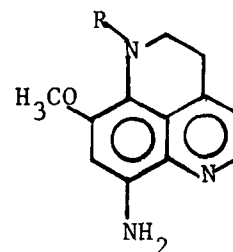
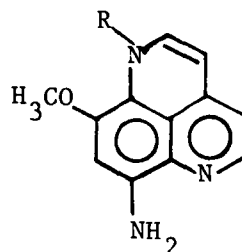
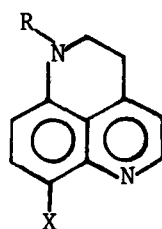
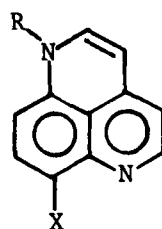
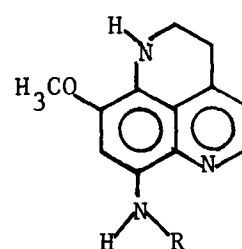
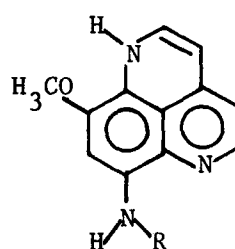
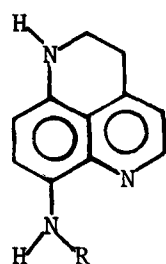
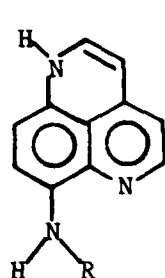
54 (400 mg)

BJ86012( $\frac{8.3}{6.3}$ , toxic)

This compound was a yellow-brown solid when it was mailed to Walter Reed Army Research Institute; however, Mr. Musallam pointed out it was a black gummy solid on arrival, hence the lack of activity may be due to decomposition which occurred in transit.

## B. Work in Progress

1. Eventual Type of Target Compounds

X=H or NH<sub>2</sub>X=H or NH<sub>2</sub>

Series A

Series B

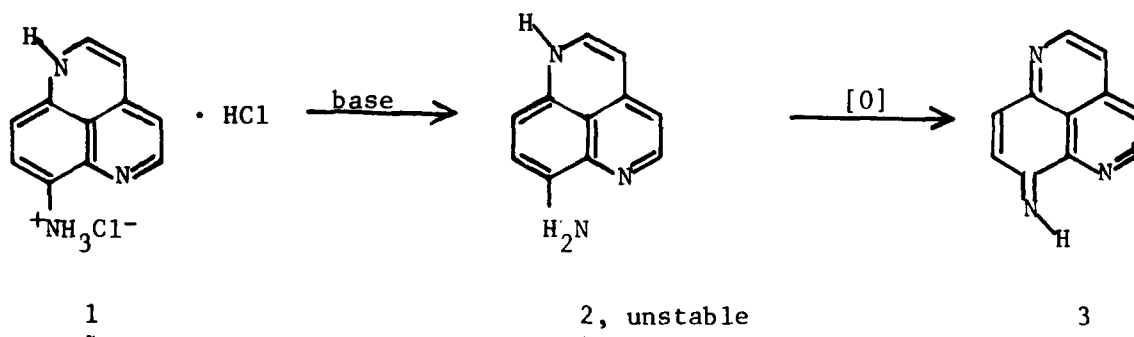
R=antimalarial effective side chain

R=antimalarial effective side chain

## 2. Immediate Goals

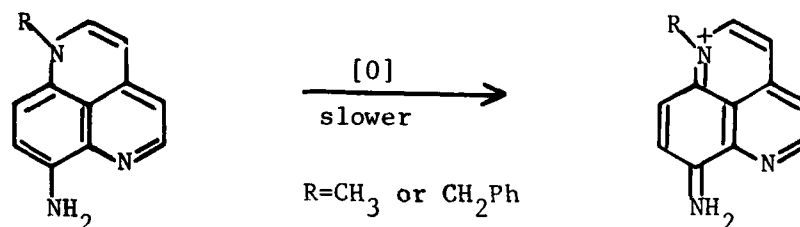
One of the key intermediates 7-amino-1,6-diazaphenanthrene dihydrochloride (1), was prepared over a year ago and characterized; however, this material (1) has been found to be unstable when converted to the free base 2, as illustrated below. It is not surprising that 7-amino-1,6-diazaphenanthrene (2) undergoes oxidation for

Scheme I



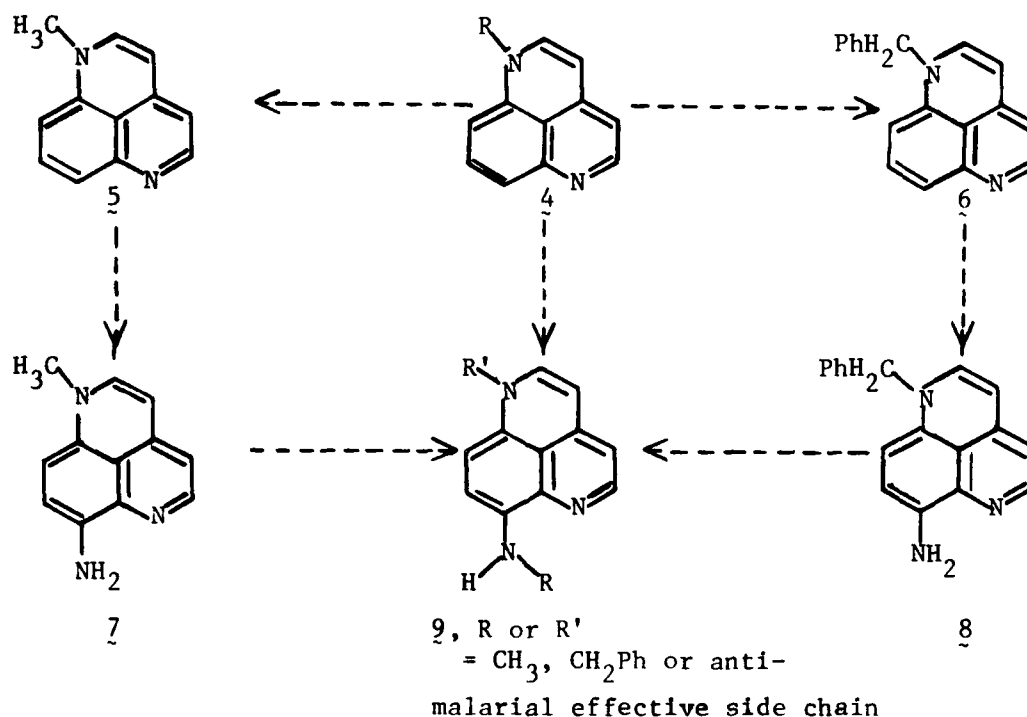
the rationale for much of this work was based on this transformation in the animal similar to the suggested activity of 8-aminoquinolines.<sup>1</sup> However, due to the instability of the free base **2** it has not been possible to alkylate this material either by treatment with alkylhalides or reductive alkylation ( $\text{RCHO}$ ,  $\text{NaCNBH}_3$ ;  $\text{RCHO}$ ,  $\text{Pd/C}$ ,  $\text{H}_2$ ). Since oxidation of **2** is so facile, it was felt that conversion of 1,6-diazaphenalene (**4**) to 1-methyl-7-amino-1,6-diazaphenalene (**5**) or to the

Scheme II



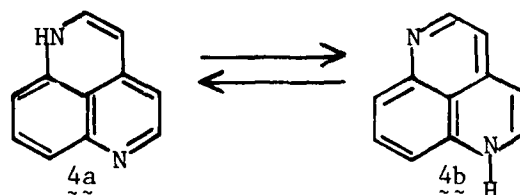
corresponding 1-benzyl derivative (**6**) might provide a template more stable to oxidation. In addition, to effectively convert 1,6-diazaphenalene (**5**) into target compounds of the type outlined in B.1. above, it was felt an extensive study

Scheme III



of the chemistry of 1,6-diazaphenalene was necessary. Our hypothesis was then to study the reactions of **4** in the hope of finding a method to obtain either **7** or **8** in high yield and in a form which could be easily converted to targets similar to **9**. The immediate goals were then to develop methods for the acylation or alkylation of **4** at position-1, followed by incorporation of functionality into position-7 of 1,6-diazaphenalene **4** which could later be converted to the 7-amino-butylamino targets outlined under B.1. (see **9** in Scheme III). One further point needs to be made in terms of the chemistry of 1,6-diazaphenalene (**4**) and that is based on the rapid proton transfer earlier<sup>2a,b</sup> shown to occur between **4a** and

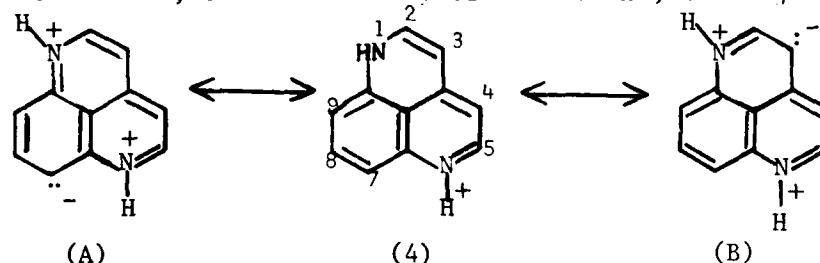
4b. This type of behavior imparts imidazole-like character to 4 and must be



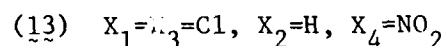
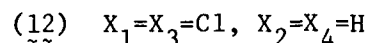
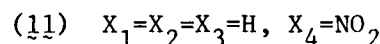
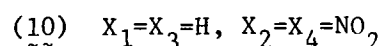
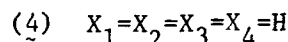
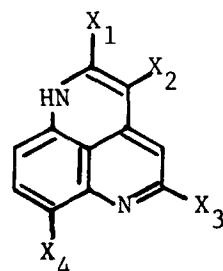
considered when developing a strategy for preparation of targets such as 9.

### Electrophilic substitution

When 1,6-diazaphenalene 4 was stirred with nitric acid in solvents such as acetic or sulfuric acid, under a variety of conditions, the major product was



always 3,7-dinitro-1,6-diazaphenalene (10) with only trace amounts of the 7-mononitro derivative (11) present. The failure to isolate significant amounts of the mononitro derivative (11) was not unexpected, for it is quite difficult to mononitrate imidazole.<sup>3</sup> Milder conditions, therefore, were required under which to

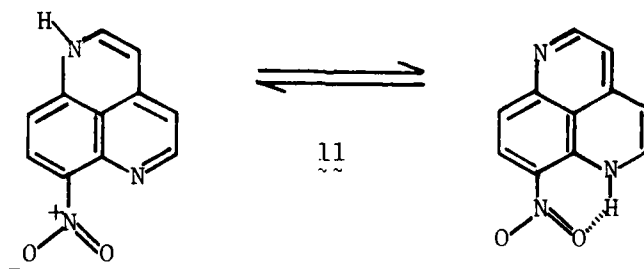


perform the nitration. It has been proposed<sup>4</sup> that nitration of aromatic substrates with sodium nitrite in the presence of trifluoroacetic acid, proceeds through the weaker electrophile  $NO^+$  rather than  $NO_2^+$ , consequently, attention was turned in this direction. In fact, when equimolar amounts of sodium nitrite and (4) were stirred at  $-60^\circ C$  in a solution of trifluoroacetic acid/chloroform, the major product (68% yield) was 7-nitro-1,6-diazaphenalene (11). There were also traces of another mononitro derivative present, as well as, some dinitro derivatives; however, no effort has been made to characterize those compounds formed in only trace quantities. The structure of (11) was based on spectroscopy. The following signals observed in the NMR spectrum of the material (11) are characteristic of 7-substituted 1,6-diazaphenalenenes:  $\delta 7.27$  (d, 2H,  $J=7Hz$ ),  $7.58$  (d, 1H,  $J=9Hz$ ),  $8.20$  (d, 1H,  $J=7Hz$ ),  $8.42$  (d, 1H,  $J=7Hz$ ) and  $9.01$  (d, 1H,  $J=9Hz$ ). While the set of five one-proton doublets in the proton NMR were quite consistent with the structure of (11), comparison of the chemical shifts and coupling constants of (11) with those of authentic 2,5-dichloro-1,6-diazaphenalene (12)<sup>5</sup> and 7-nitro-2,5-dichloro-1,6-diazaphenalene (13)<sup>5</sup> also served to support the structure of (11). The 7-nitro-dichlorodiazaphenalene (13) had been prepared previously by treatment of (12)<sup>5</sup> under

conditions (TFAA/ $\text{NaNO}_2$ ) analogous to those discussed above. Apparently, under the milder nitration conditions, the mononitro derivative (11) was formed predominantly from (4). This served to indicate the pyridine nitrogen of (4) was protonated and electrophilic substitution occurred by way of resonance structure (A). This was not surprising since protonation of the pyridine portion of (4) serves to deactivate this ring to electrophilic attack,<sup>6</sup> while electron release from position -1 activates position -7 to reaction. It must be remembered that both nitrogen containing rings of 1,6-diazaphenalene (4) at one time or another have pyridine character ( $4a \rightleftharpoons 4b$ ) and hence would be deactivated to an equal extent in trifluoroacetic acid. Moreover, because of the rapid tautomerism of the type discussed above, positions -3 and -4 can be considered equivalent; in like manner positions -7 and -9 are interchangeable. For this reason, nitration of (4) at either position -7 or -9 leads to the same mononitro derivative (11).

Even though the spectral data, including the 60 MHz NMR spectrum, supported the structure of (11). The 220 MHz spectrum of this material, however, contained an unusual coupling pattern [see Experimental for actual 220 MHz spectrum of (11)],  $\delta$ 7.27 (d, 1H,  $J=6.5\text{Hz}$ ), 7.29 (d, 1H,  $J=7\text{Hz}$ ), 7.58 (d, 1H,  $J=9.5\text{Hz}$ ), 8.20 (t, 1H,  $J=6.5\text{Hz}$ ), 8.42 (t, 1H,  $J=7\text{Hz}$ ), 9.01 (d, 1H,  $J=9.5\text{Hz}$ ). The signals at  $\delta$ 9.01 and 7.58 have been assigned to protons -8 and -9 while resonance lines at  $\delta$ 8.42 and 7.29 were assigned to protons -5 and -4. In addition the signals located at  $\delta$ 8.42 and 7.27 were assigned to protons -2 and -3, respectively. The above assignments were based on the chemical shifts and coupling constants observed in the proton spectrum; however, the protons at  $\delta$ 8.20 (proton -2) and 8.42 (proton -5) appeared as triplets which was unusual and may be explained as follows: Substitution of the nitro group destroys the symmetry of the molecule but in the T-60 NMR spectrum the proton transfers between molecules rapidly enough to provide a spectrum composed of the average of the two molecules. In the 220 MHz spectrum, however, the rate of tautomerism became slower with respect to the NMR scale and the spectrum of both forms became visible. This led to the two triplets at  $\delta$ 8.20 and 8.42, the rest of the signals remaining undisturbed.

In fact, the less rapid proton transfer in the 7-nitro derivative 11, in comparison to that known to occur in 4, may occur because the oxygen of the nitro group lies near the peri proton of 11, and a pseudo six-membered ring has been formed by way of H-bonding. The proton is therefore retained longer at position -6 as illustrated here:

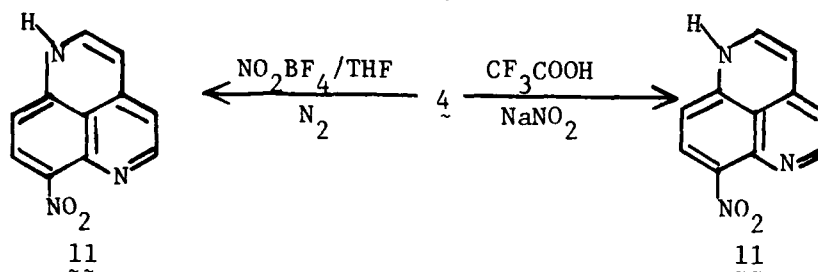


In the above case, there would be two compounds which would exist in solution, for the proton may be attached to either position -1 or -6 of 11 for a finite length of time to permit recording of the spectrum for both compounds. In order to study this point, the C-13 NMR spectra of 1,6-diazaphenalene (4) and of 7-nitro-1,6-diazaphenalene (11) were recorded. The carbon spectrum of 4 contained only seven peaks because the proton transfer ( $4a \rightleftharpoons 4b$ ) resulted in a symmetrical molecule [146.4, 144.4, 140.4, 127.3, 113.7, 113.0 and 111.3 ppm], while the C-13 NMR spectrum of (11) contained a much more complicated pattern of 18 peaks [151.8, 145.7, 145.5, 145.3, 141.8, 141.6, 137.1, 136.8, 136.6, 133.6, 127.4, 123.2, 122.8, 111.9, 111.8, 110.1, 108.7 and 94.47 ppm]. The number of lines present in the spectrum of (11) did indicate that two compounds do exist, although, a few of the

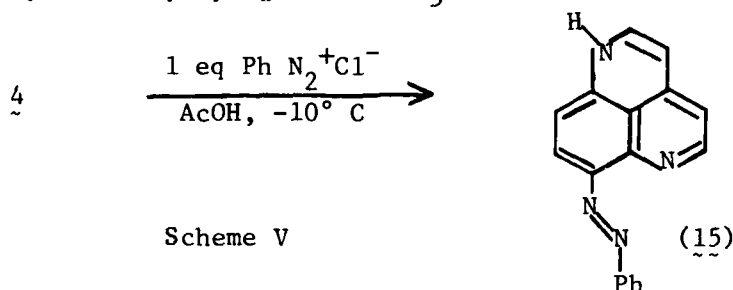
signals did overlap. In order to further clarify this picture of proton transfer, methylation of 7-nitro-1,6-diazaphenalene (29) was performed.<sup>7</sup> The 7-nitro compound was reacted with LDA followed by treatment of the anion with methyl iodide to yield N-methyl-7-nitro-1,6-diazaphenalene (14). The high resolution NMR spectrum (100 MHz) of this compound clearly contained only three sets of doublets [ 7.20, (1H, d, J=7Hz), 7.26 (1H, d, J=7Hz), 7.40 (1H, d, J=9.5Hz), 8.18 (1H, d, J=7Hz), 8.28 (1H, d, J=7Hz) and 8.95 (1H, d, J=9.5Hz)], which indicated that substitution of the proton with a methyl group had indeed prohibited tautomerism. This resulted in the appearance of signals of only one compound in the NMR spectrum of the N-methyl derivative.

In a related study, 1,6-diazaphenalene (4) was reacted with nitronium tetrafluoroborate ( $\text{NO}_2\text{BF}_4$ ) in tetrahydrofuran under nitrogen, to provide a moderate (48%) yield of (11). Despite the lower yield, this reaction could be carried out with less difficulty since the workup was much easier and (11) was the sole product (Scheme IV).

Scheme IV



In order to compare the reactivity of 11 toward weak electrophiles as opposed to nitronium ions, 4 was reacted with phenyldiazonium chloride, according to the method for Heidelberg.<sup>8</sup> From this process, one major compound 15 was isolated; the CI mass spectrum of which indicated a monophenyldiazonium adduct had been obtained. The NMR spectrum of (15) was quite complex, consequently, the sequence was repeated employing aniline- $\text{d}_5$  as the source of the diazonium electrophile.

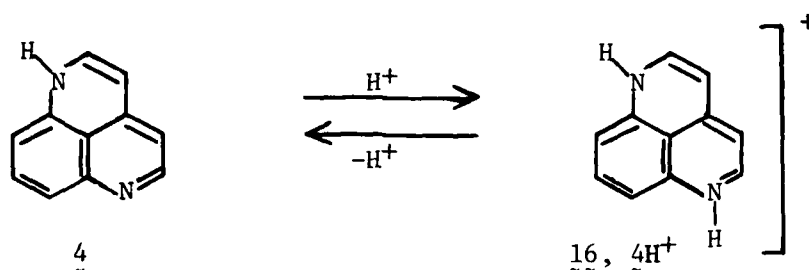


Scheme V

As above, only one product was obtained, furthermore this material possessed similar characteristics to 15. The parent ion in the CI mass spectrum of this azocompound was observed at 278 ( $\text{M}^++1$ ) mass units which corresponded to the formula of the monosubstituted- $\text{d}_5$  product, moreover, the NMR spectrum of 15- $\text{d}_5$  contained clearly three sets of AB doublets [ $\delta$ 6.50(J=7Hz), 6.82(J=7Hz), 7.27(J=8Hz), 7.58(J=8Hz), 8.10(J=7Hz) and 8.52(J=7Hz)] which indicate, unambiguously, that 15- $\text{d}_5$  was 7-phenyl( $\text{d}_5$ )-azo-1,6-diazaphenalene. The weak electrophile, under the conditions of Heidelberg,<sup>8</sup> (aq HCl) had therefore attacked position -7 of 4 to provide the 7-substituted derivative 15 quite similar, in fact, to the nitration of 4 with sodium nitrite (TFAA) or with nitronium fluoroborate.

In contrast to the behavior of 4 toward nitration in acidic solution, the 2-3 double bond (B) was the most reactive position of the molecule in a medium of lesser acidity. This investigation has centered on the reaction of bromine with the neutral molecule (4) and, where possible, the analogous transformation has been





carried out on the protonated form (16) of 1,6-diazaphenalene.

When 1,6-diazaphenalene (4) was reacted with bromine in the presence of sodium acetate [1:40 ratio of (4) to sodium acetate], under conditions analogous to the bromination of imidazole,<sup>9</sup> the tribromo derivatives 3,4,7-tribromo-1,6-diazaphenalene (17) and 2,3,4-tribromo-1,6-diazaphenalene (18) were formed. The proton NMR spectrum of (17), run at 60 mHz, contained a set of AB doublets [ $\delta$ 6.20 and 7.42 ( $J=8\text{Hz}$ , protons -9 and -8)] and two singlets [ $\delta$ 7.88 and 8.26 (protons -5 and -2)] while the NMR spectrum of (18) had two doublets [ $\delta$ 6.22 and 7.58 (protons -9 and -7,  $J=8\text{Hz}$ )] and a triplet centered at  $\delta$ 7.40 ( $J=8\text{Hz}$ , proton -8). The coupling pattern of the latter indicated that three protons ( $J=8\text{Hz}$ ) were coupled to each other, moreover, a singlet was also present in the spectrum of (18) at  $\delta$ 8.02 (proton -5). The above evidence coupled with infrared spectroscopy and mass spectroscopy supported the assignment of structures (17) and (18) as correct representations of these molecules. Significant amounts of the 2,3-dibromo derivative (19) accompanied (17) and (18) in the mixture. The mass spectrum of the dibromo derivative (19) contained a parent peak at 327 ( $M^++1$ ) mass units, moreover the proton spectrum fully supported the structure of (19) for this material [ $\delta$ 7.08 and 8.51 ( $J=7\text{Hz}$ , proton -9 and -7), 7.42 and 8.26 ( $J=9\text{Hz}$ , proton -4 and -5) and a triplet at 8.18 ( $J=7\text{Hz}$ ; proton -8)]. The yields (Table I) under these conditions (one equivalent of bromine) were low due to the recovery of starting (4), and the formation of small

SCHEME VI

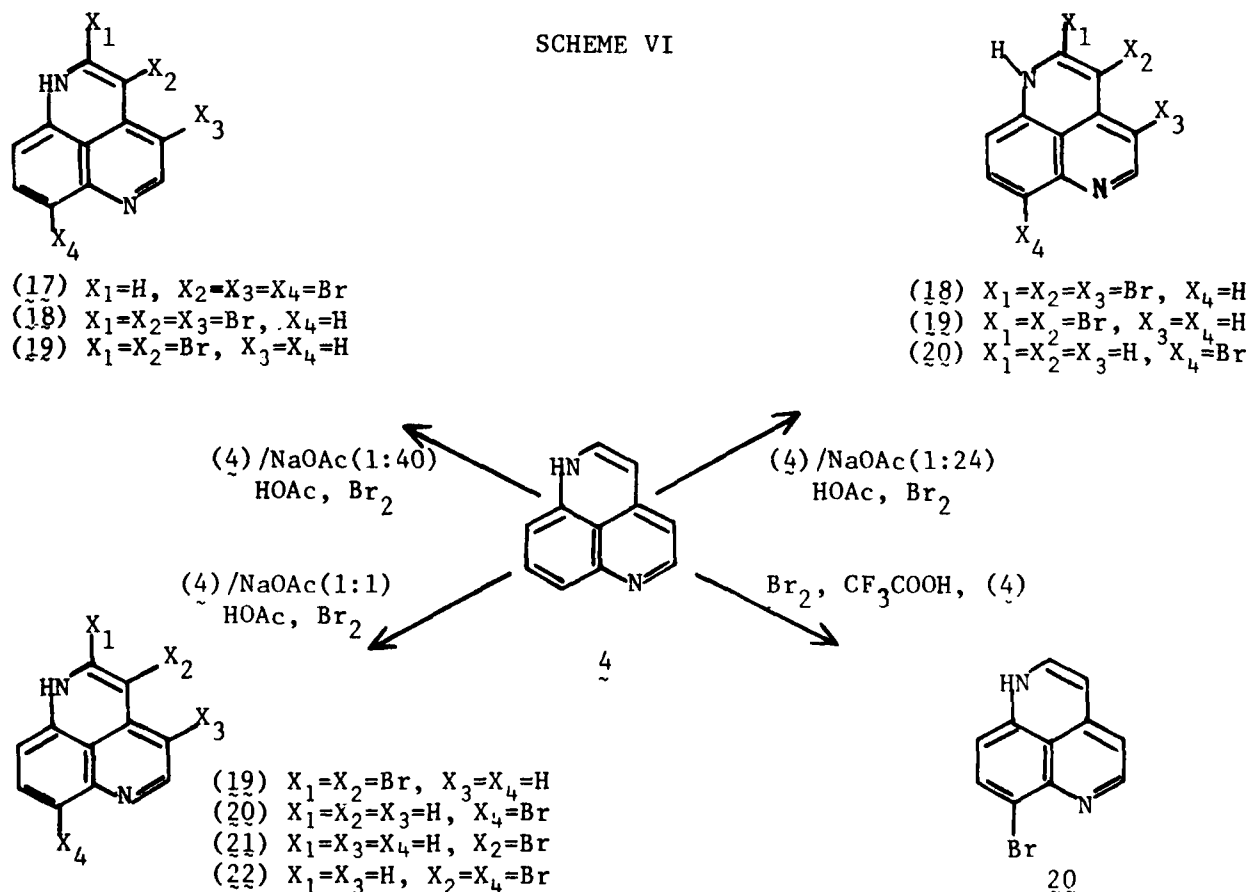


Table I. Bromination of 1,6-Diazaphenylene

Substrate	Conditions <sup>a</sup>	Products [yield %] <sup>e</sup>
(4)	Br <sub>2</sub> , NaOAc (1:40) <sup>b</sup> HOAc	(17) [10.5]; (18) [6.2]; (19) [5.1]; others [trace]
(4)	Br <sub>2</sub> , NaOAc (1:24) HOAc	(18) [8.0]; (19) [6.3]; (20) [4.16]; others [trace]
(4)	Br <sub>2</sub> , NaOAc (1:1) HOAc	(20) [9.5]; (19) [6.1]; (21) [4.0]; (22) [3.1]
(4)	Br <sub>2</sub> , NaOAc (1:24) HOAc <sup>c</sup>	(19) [11.8]; (18) [2.1]; others [trace]
(4)	Br <sub>2</sub> (1/2 eq, 1:20) HOAc	(21) [11.4]; (20) [7.7]; (22) [trace]; (19) [trace]
(4)	Br <sub>2</sub> , CF <sub>3</sub> COOH, CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>	(20) [81.0]; others [trace]

<sup>a</sup>Reactions were carried out at room temperature unless otherwise indicated.

<sup>b</sup>The ratio set in parenthesis is the ratio of (4) to sodium acetate employed in the experiment.

<sup>c</sup> -10°C. <sup>d</sup> -60°C. Similar results were observed at room temperature. <sup>e</sup>The yields in the reactions with bromine are low because of difficulties encountered during separation of these materials; however, the relative amounts of the isomers present are quite representative, as indicated.

quantities of four other halo isomers. When the ratio of (4) to sodium acetate was altered to 1:24, the 2,3,4-tribromo and 2,3-dibromo derivatives (18) and (19), respectively, comprised much of the product mixture. In addition, however, a small amount of 7-bromo-1,6-diazaphenalene (20) was now isolated, as well as starting (4). The CI mass spectrum of (20) contained a parent ion at 248 ( $M^+ + 1$ ) mass units indicative of the incorporation of one bromine atom into the molecule, while the proton NMR spectrum contained three sets of AB doublets at 6.35 ( $J=5\text{Hz}$ , proton -3), 8.20 ( $J=5\text{Hz}$ , proton -2), 6.15 ( $J=7\text{Hz}$ , proton -4), 7.40 ( $J=7\text{Hz}$ , proton -5), 6.60 ( $J=8\text{Hz}$ , proton -9) and 7.64 Hz ( $J=8\text{Hz}$ , proton -8), respectively. Since the excess sodium acetate in acetic acid served to neutralize any hydrogen bromide generated in the process, the conditions described above dealt essentially with the neutral species (4).

In order to study the reaction under more acidic conditions, the ratio of (4) to sodium acetate was then altered to 1:1, as illustrated in Scheme VI. The 7-bromo-1,6-diazaphenalene (20) now became the major product which was isolated along with diazaphenalenenes (19) and (22), as well as a new monobromo derivative, 3-bromo-1,6-diazaphenalene (21).

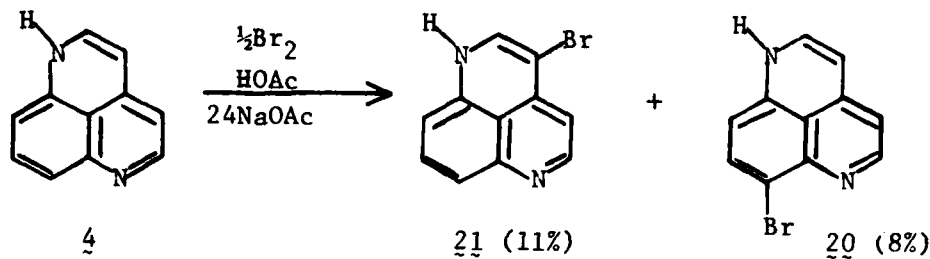
The structure of (21) was determined principally by NMR spectroscopy. The proton spectrum contained two sets of AB doublets [ $\delta 6.72$  and  $7.00$  ( $J=8\text{Hz}$ , proton -9 and -7)], a triplet at  $\delta 7.41$  ( $J=7\text{Hz}$ , proton -8) and a singlet at  $\delta 8.15$  (C-2). This resonance pattern coupled with mechanistic considerations are consistent only with structure (21). Moreover, the 3,7-dibromo derivative (22) was shown to contain two bromine atoms by CI mass spectroscopy [ $327 (M+1)$ ], while the NMR spectrum contained two sets of AB doublets [ $6.42$  and  $8.04$  ( $J=7\text{Hz}$ , proton -4 and -5);  $7.21$  and  $7.55$  ( $J=8\text{Hz}$ , proton -8 and -9)] and a singlet at  $\delta 8.61$  (proton -2). As mentioned above, 7-bromo-1,6-diazaphenalene (20) now became the major product at the expense of the 2,3- and 2,3,4-halo isomers previously found.

The trend appeared clear at this point, the more acidic reaction medium definitely favored formation of the 7-bromo-diazaphenalene (20) in preference to the other isomers. The change in orientation during electrophilic substitution of protonated versus neutral pyridines and quinolines has been reported<sup>6</sup> while this is similar to results described herein, caution must be exercised at this juncture in direct extrapolation of this phenomenon to that of 1,6-diazaphenalene.

Earlier on examination of the NMR spectrum of (4)<sup>2b</sup> it had been found that this base, as expected, was protonated in trifluoroacetic acid, consequently it was felt this reagent would provide a medium with which to brominate the protonated species (16). In complete agreement with this hypothesis, the bromination of 1,6-diazaphenalene in trifluoroacetic acid gave an 81% yield of 7-bromo-1,6-diazaphenalene (20, see Scheme VI). This follows directly the event described above, and served to illustrate that halogenation of (16) should occur preferably at the 7-position of the molecule, in contrast to the substitution pattern observed on the neutral species (4).

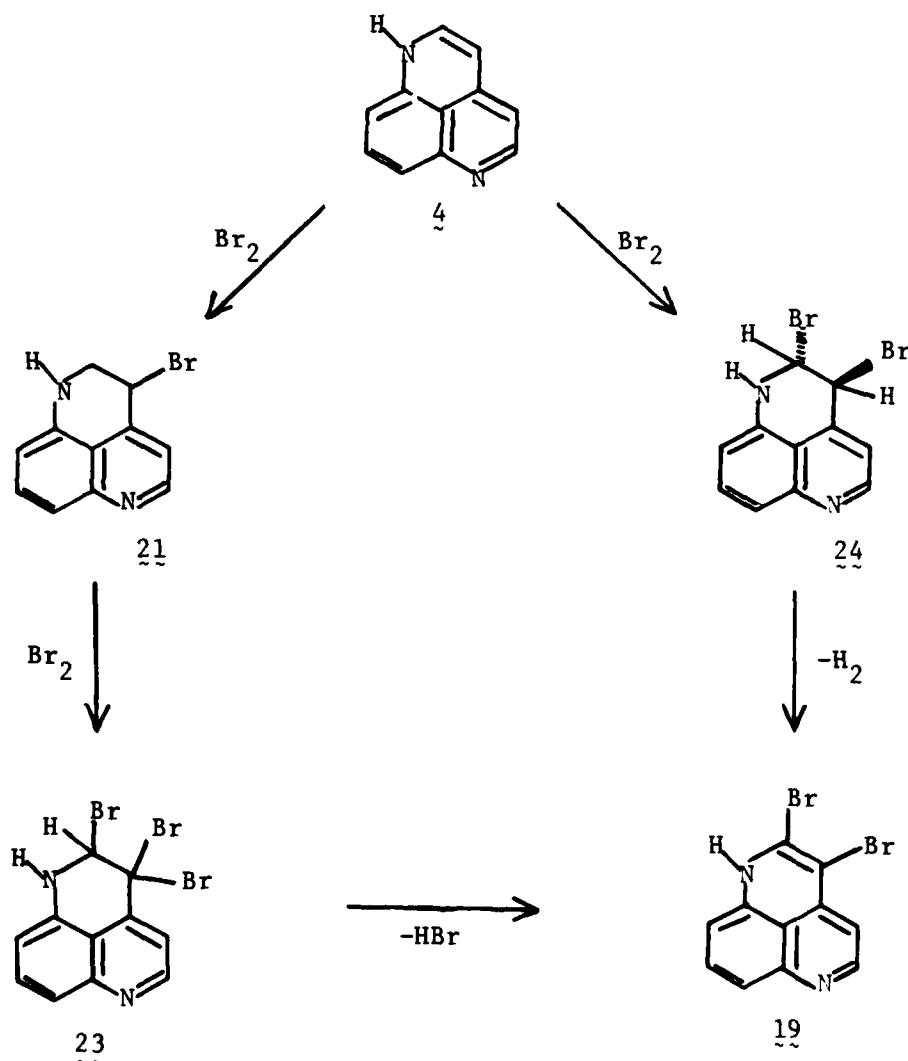
While attack of an electrophile on either position -3 or -7 of (4) is not exceptional and has been discussed,<sup>5</sup> the formation of 2,3-disubstituted derivative 19 deserves some comment. Two possible pathways for the formation of the dibromo isomer 19 are shown in Scheme VII. The path  $4 \rightarrow 21 \rightarrow 23 \rightarrow 19$  first involves substitution of bromine at position -3, followed by addition of  $\text{Br}_2$  across the 2-3 double bond. Elimination of  $\text{HBr}$  would then generate 19. Support for the supposition that the 3-bromo derivative 21 is formed first comes from INDO calculations,<sup>10</sup> and additional experimental evidence.

When the base 4 was treated with half an equivalent of bromine, the major product was the 3-bromo-1,6-diazaphenalene 21 which was not isolated in substantial quantities when one equivalent of bromine was used. The other major product was the 7-bromo isomer 20, as shown below.



Since bromine is an oxidizing agent, the lesser concentration of this reagent may have impeded conversion of 23 or 24 to 19;

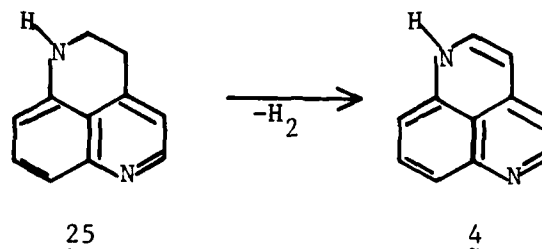
Scheme VII



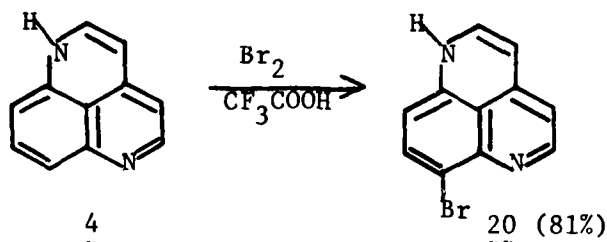
however, INDO calculations indicate that the 2-3 bond has the most double bond character of all the bonds in the molecule, and substitution of a halogen at the 3 position only decreases this slightly. The highest degree of polarization in the molecule, considering both total electron densities and HOMO densities is between the carbon atoms in the 2 and 3 positions. These factors should favor the addition of  $\text{Br}_2$  across the 2-3 double bond. A 2,3,3-tribromo diazaphenalene such

as 23 has never been observed; however, the lack of stability for such a specie might be expected to prevent isolation.

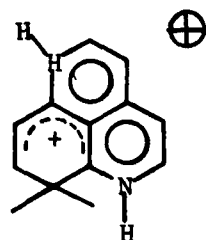
The alternate pathway,  $1 \rightarrow 24 \rightarrow 19$  involves addition of  $\text{Br}_2$  across the 2-3 double bond first, followed by loss of  $\text{H}_2$ . While 2,3-dihydro-1,6-diazaphenalene 25 reverts to 4 upon standing for prolonged periods,<sup>5</sup> one might expect loss of  $\text{HBr}$  to be a more favorable process in the case of the dibromide 24. If this were the case, one would expect to isolate both the 2-bromo and 3-bromo isomers. It is important to note that 2-bromo-1,6-diazaphenalene has never been observed in work carried out to date, and the only compounds obtained with a bromine in the 2-position were also substituted with bromine at the 3 position. Thus, the path  $1 \rightarrow 21 \rightarrow 23 \rightarrow 19$  appears to be the most reasonable.



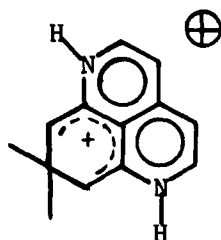
In keeping with the desired to convert 4 into potential antimalarial agents,<sup>2b</sup> a number of methods have been examined to incorporate functionality into position-7 of 4. Since halogen has been displaced by amines in the quinoline series<sup>11</sup> and also can undergo lithium-halogen exchange to generate a carbanionic center, this group appeared very useful as a precursor to other 7-substituted-1,6-diazaphenalenenes. From the results previously discussed it is obvious that increased acidity favors the formation of the 7-substituted product. It has also been shown that 1,6-diazaphenalene was protonated to yield the cation 2 in trifluoroacetic acid.<sup>2b</sup> Without exception reactions carried out in this medium resulted



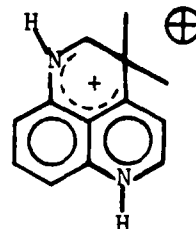
in the almost exclusive formation of the 7-substituted product.<sup>12</sup> In the case of the protonated diazaphenalene 16; however, the comparable electron densities of the 3 and 7-positions argue against exclusive substitution. We therefore utilized the Wheland model of the transition state<sup>13</sup> to calculate  $\pi$  localization energies ( $\pi$  bonding between the atom undergoing substitution and the rest of the molecule is cut off). Since the conjugate acid 16 of 1,6-diazaphenalene was symmetrical, calculations were only carried out for substitution at the 2,3,7- and 8-positions. The resulting localization energies indicate that the lowest energy sigma complex is reached for substitution at the 2-position, followed by substitution at positions 7(9), 8, and 3(5) in that order. Since electrophilic attack at the 2-position is electrostatically unlikely, the result that substitution at position 7(9) is favored over the other possibilities is in complete agreement with the experimental observations. The localization energies relative to substitution at position-7 are given below (see Figures 1-9 for complete details).<sup>10</sup>



0 Kcal/mol



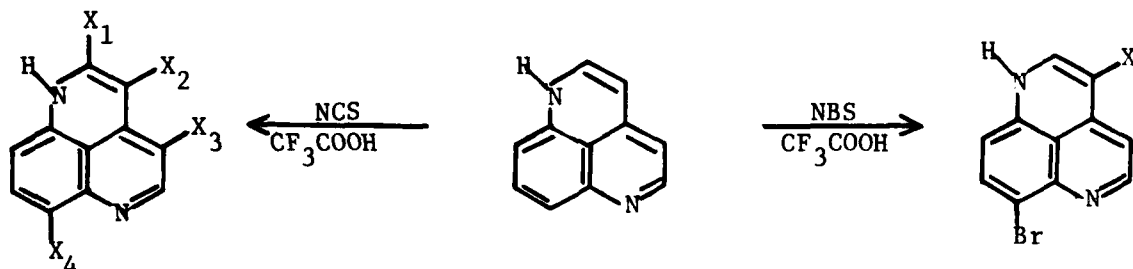
7 Kcal/mol



21 Kcal/mol

Although the reaction of (4) with chlorine or iodine would be expected to be troublesome, experimentally; the above results in the bromine area did provide a solution to this problem. Since it was known that (16) preferentially reacted at position -7 with bromine, a 1:1 mixture of 1,6-diazaphenalene (4) and N-bromosuccinimide<sup>14</sup> was stirred in trifluoroacetic acid; this procedure cleanly furnished a 64.8% yield of the 7-bromo compound (20). Simple extrapolation of this technique to N-chlorosuccinimide did provide 7-chloro-1,6-diazaphenalene (25). Since both chlorine and the chloronium ion are more reactive toward electrophilic substitution<sup>15,16</sup> than the corresponding bromine analogs, it was not surprising that substantial amounts of (26), (27) and (28) [Scheme VIII] were formed under these conditions (yields shown in Table II).

## SCHEME VIII

(25)  $X_1=X_2=X_3=H$ ,  $X_4=Cl$ 

(4)

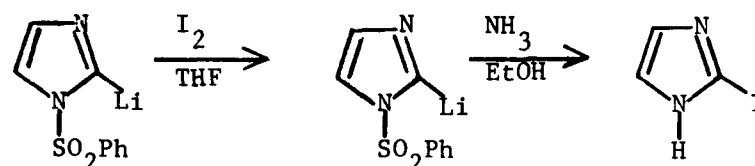
(20)  $X=H$ (26)  $X_1=X_3=X_4=H$ ,  $X_2=Cl$ (29)  $X=Br$  (trace)(27)  $X_1=X_2=Cl$ ,  $X_3=X_4=H$ (28)  $X_1=X_3=H$ ,  $X_2=X_4=Cl$ 

Table 2. Reaction of 1,6-Diazaphenalene with N-Halosuccinimides

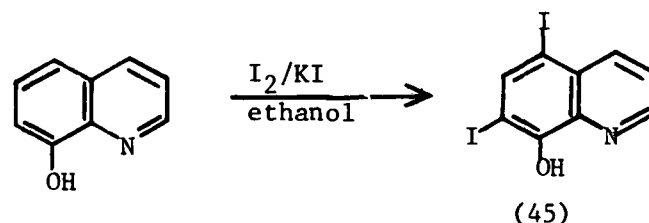
Substrate	Conditions	Products [yield %]
(4)	NBS, $CF_3CO_2H$ , $CH_2Cl_2$	(20) [64.8] (20) [trace]
(4)	NCS, $CF_3CO_2H$ , $CH_2Cl_2$	(25) [33.5] (26) [27]
		(27) [11.5] (28) [7.9]
(4)	NIS, $CF_3CO_2H$ , $CH_2Cl_2$	(30) [45.6] (31) [trace]

Although the separation of the chlorinated diazaphenalenenes was very difficult, high pressure liquid chromatography was found to be an effective tool in this regard. The structures of the chlorinated diazaphenalenenes 25-28 were deduced by comparison of the NMR, IR and mass spectral data obtained on these compounds to those observed for the corresponding bromo derivatives.

Iodination of (4), as with other iodination reactions has proven to be a tricky process. A number of recent approaches to the iodination of imidazole have shown some success, thus, imidazole can now be monoiodinated at C-2 via the 2-lithio derivative.<sup>17</sup>



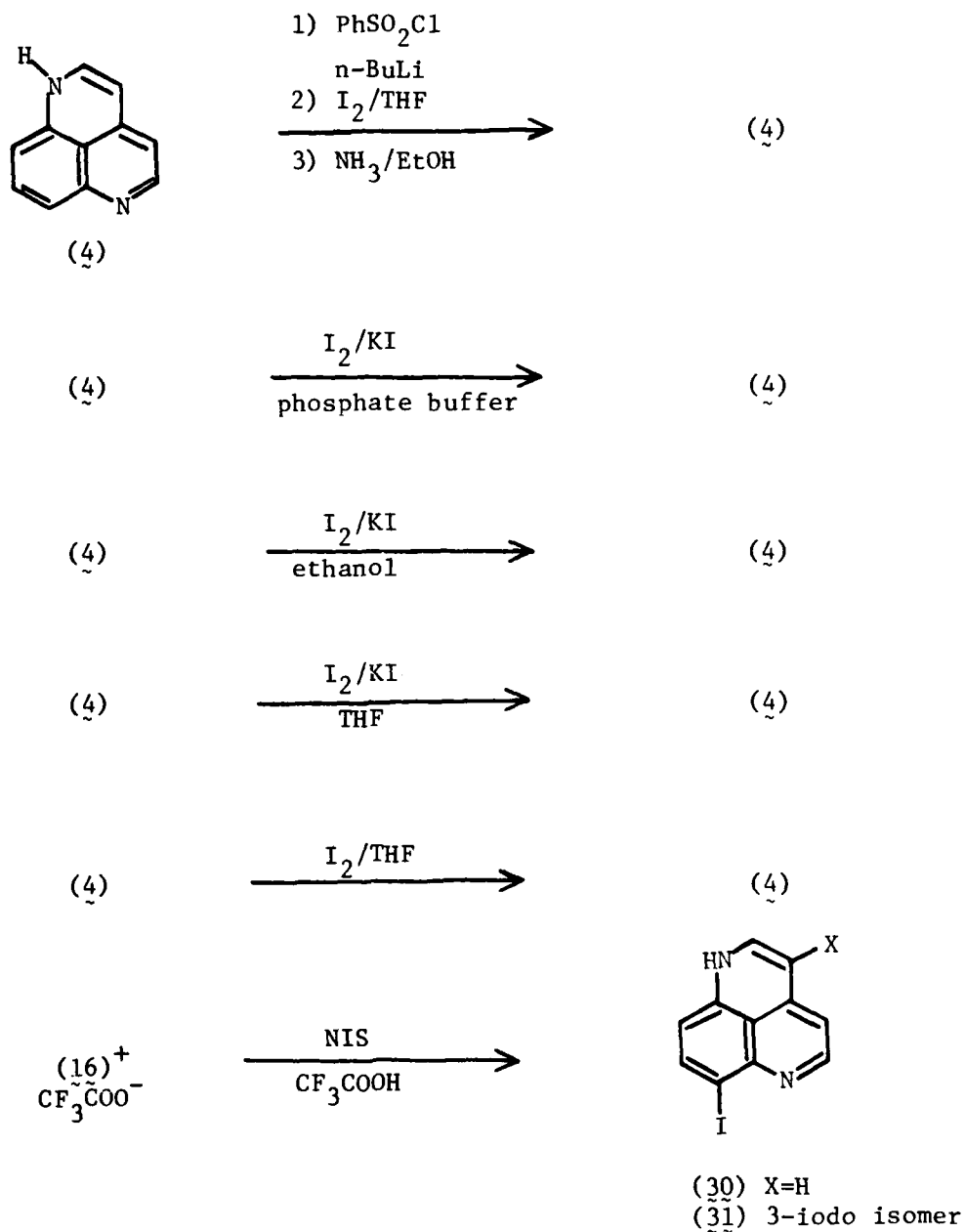
When the same procedure was attempted with 1,6-diazaphenalene (4) [dissolution of (4) in DMSO followed by addition of one equivalent of potassium hydroxide and one equivalent of benzene sulfonyl chloride at 0°C], only starting (4) was recovered. It appears that 1,6-diazaphenalene failed to undergo the phenylsulfonation step<sup>7</sup> which precluded the lithiation and iodination steps scheduled to follow. It is also known that 8-hydroxy quinolines<sup>18</sup> undergo reaction with potassium iodide in ethanol; however, upon addition of a potassium iodide solution to 1,6-diazaphenalene in ethanol, starting (4) crystallized from the medium.



The same result was obtained when tetrahydrofuran was substituted for ethanol, moreover, when potassium iodide was eliminated from the mixture, iodine itself was too inert to react with 1,6-diazaphenalene.

Despite the early difficulties encountered during attempts to iodinate (4) as illustrated in Scheme IX, simple extrapolation of the technology employed for halogenation of 1,6-diazaphenalene with N-bromo- and N-chlorosuccinimides provided a means by which to prepare 7-iodo substituted 1,6-diazaphenalene (30). A 1:1 mixture of 1,6-diazaphenalene and N-iodosuccinimide was stirred in trifluoroacetic acid, and clearly furnished a 45.6% yield of 7-iodo-1,6-diazaphenalene (30) contaminated with only trace amounts of other products such as (31); see Scheme IX. The CI mass spectrum of (30) contained a parent ion at 295 ( $M^+ + 1$ ) mass units which corresponded to the empirical formula  $C_{11}H_7N_2I$ . The proton NMR of this material contained three sets of AB doublets [6.32 and 8.06 ( $J=5\text{Hz}$ , proton -3 and -2), 5.98 and 7.22 ( $J=7\text{Hz}$ , proton -4 and -5), 6.43 and 7.81 ( $J=8\text{Hz}$ , proton -9 and -8)], which is consistent only with the structure of the 7-iodo isomer (30). Support for this assignment was also obtained by comparison of the spectrum of (30) to those of the 7-bromo and 7-chloro analogs.

## SCHEME IX



The unique character of 1,6-diazaphenalene (4) and the protonated species (16) have been thoroughly studied as to the orientation of substitution when either of these molecules is attacked by electrophiles. In agreement with theoretical calculations,<sup>10</sup> the protonated species reacts with a variety of electrophiles including  $^+\text{NO}_2$ ,  $\text{PhN}_2^+$ ,  $\text{Br}^+$ ,  $\text{Cl}^+$  and  $\text{I}^+$  to provide 7-substituted-1,6-diazaphenalenenes in moderate to very good yields. This is a fortuitous, but fortunate circumstance for the ability to selectively place a halogen substituent at position -7 of 1,6-diazaphenalene will doubtless become invaluable in future attempts to attach an aminobutylamino side chain to position -7 of 4.

#### Oxidation

Since 7-amino-1,6-diazaphenalene (2) undergoes rapid oxidation which leads to

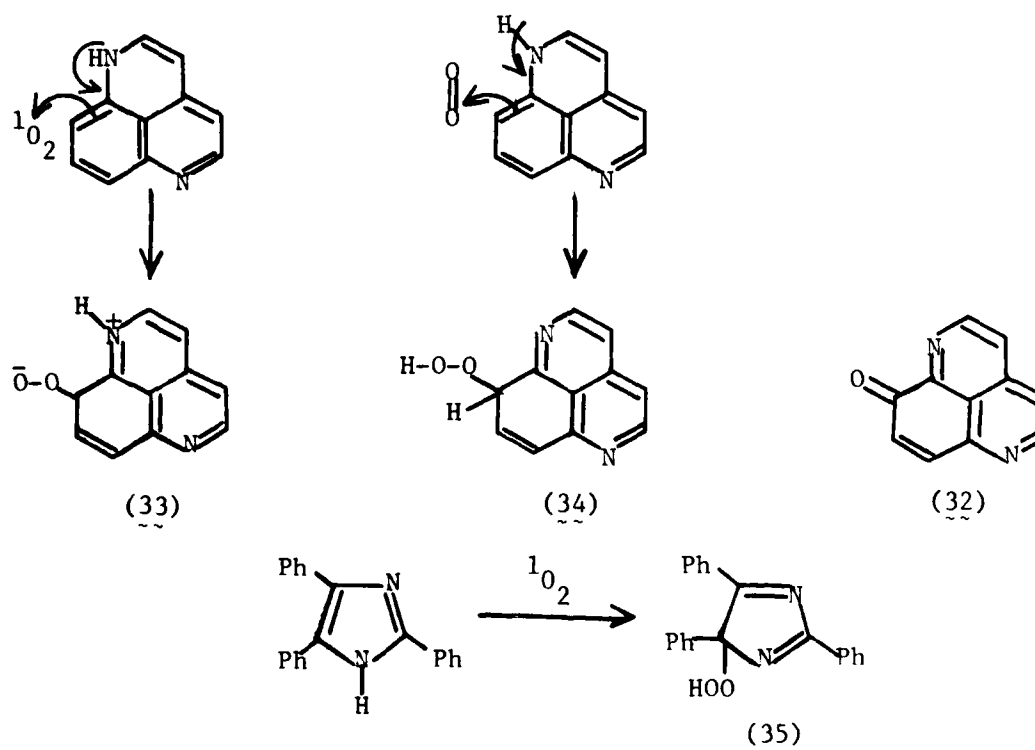


decomposition, there is special interest with regard to the oxidation of 4. In particular, the similarities between the properties of 4<sup>2a,b</sup> and imidazole prompted a study of the reaction of 4 with singlet oxygen in analogous fashion to that previously reported for imidazole (Dye-sensitized photooxidation).<sup>19</sup>

Like many electron-rich heterocyclic systems such as pyrroles and imidazoles,<sup>19</sup> 4 suffered extensive decomposition when reacted with oxygen, in the presence of Rose Bengal and light (650W tungsten-halogen lamp) under moderate concentrations of chloroform/ethanol. On the other hand, in dilute solution (100 mg in 500 ml of solution) the photooxygenation took place smoothly to provide a single product (32) in 50% yield.

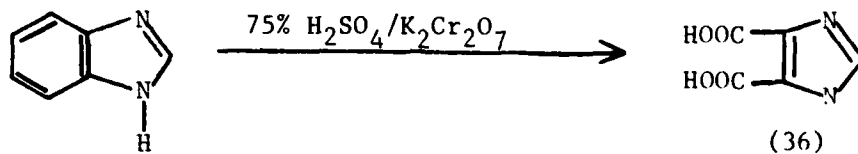
In Scheme X, the uptake of oxygen is pictured to occur at the 7-position (i.e., same as position -9) of (4) as an ene-like reaction facilitated by electron release from the nitrogen at position -1. Electron availability at C-3 might have rendered this position a competitive site for attack by the electrophilic oxygen, but reaction at C-7 has the advantage (peri position) of a favorable 6-membered transition state for C-O bond formation coincident with the breaking up of the N-H bond. Alternatively, a zwitterionic product (53) may be initially formed by release of electrons to oxygen from the enamine. Formed by either process, the intermediate hydroperoxide (34) would then suffer ready dehydration to yield the observed ketone (32). Loss of water would be expected to take place readily from (34) since the proton at C-9 of the hydroperoxide is relatively acidic. It is interesting to note that hydroperoxides of type (35) are

SCHEME X



formed as intermediates in the photooxygenation of arylimidazoles.<sup>20</sup>

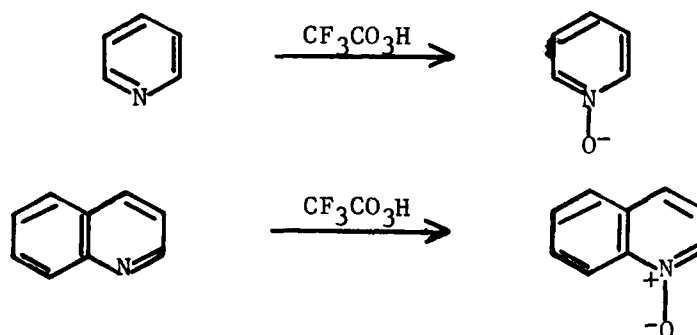
In relation to this study, reaction of (4) with other oxidizing agents has been explored. It has been reported that benzimidazole<sup>21</sup> reacted with 75%  $H_2SO_4/K_2Cr_2O_7$  to provide imidazole-4,5-dicarboxylic acid (36) in 55% yield. A similar oxidation was attempted with 1,6-diazaphenalene (4), however, this procedure gave



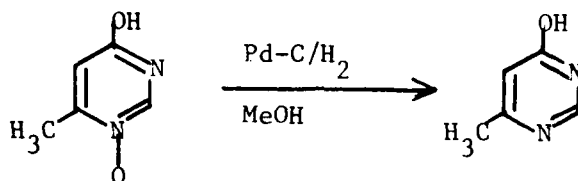
only decomposition products. Moreover, when 30%  $\text{H}_2\text{SO}_4$  was employed instead of 75%  $\text{H}_2\text{SO}_4$ , only starting (4) was recovered.

Sharpless has reported work on allylic oxidations which employed selenium dioxide and a peroxide.<sup>22</sup> This reagent proved to be very useful in our laboratory in the indole area,<sup>23</sup> but when (4) was treated in this fashion<sup>23</sup> at least eight products were observed on TLC. No effort has been made to characterize the compounds because of the difficulty encountered in isolation of these very polar materials.

Because of their selectivity, solubility in organic solvents, innocuous reduction fragments, and susceptibility to simple quantitative analysis, hydrogen peroxide and its organic derivatives have found extensive application as oxidants in organic synthesis.<sup>24</sup> It has also been reported that certain heterocyclic compounds react rapidly and exothermally with trifluoroperacetic acid but not in the same fashion as their hydrocarbon analogs. For instance, pyridine and quinoline react quickly to form the corresponding amine N-oxide.<sup>25</sup>

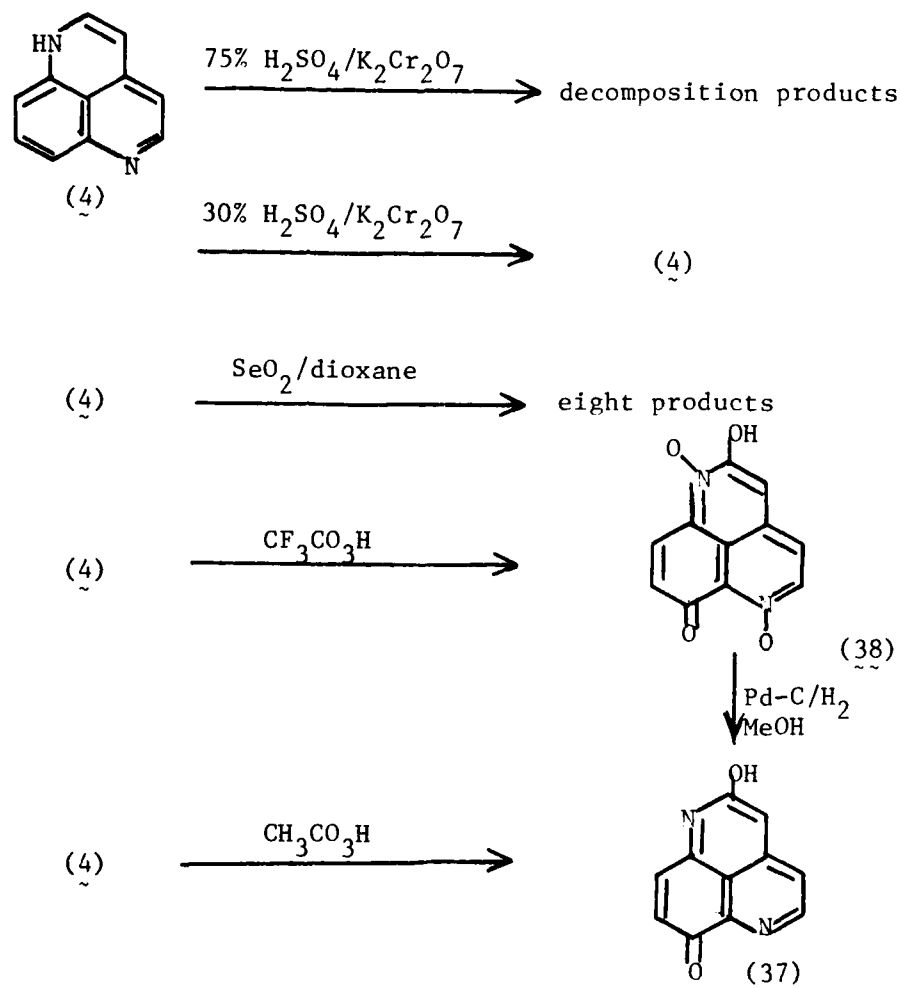


Further oxidation can provide ring-fission products such as muconic and fumaric acids. In view of the literature on peracids 1,6-diazaphenalene (4) was refluxed in excess peracetic acid for 2 h after which a brick-red compound (37) was obtained. The parent peak in the CI mass spectrum of (37) was observed at 199 ( $M^+ + 1$ ) mass units, while the infrared spectrum contained characteristic bands at 1680 ( $\text{C}=\text{O}$  absorption), and 3100 ( $\text{O}-\text{H}$  stretch),  $\text{cm}^{-1}$ . In addition the proton NMR spectrum of (37) contained one singlet ( $\delta 7.00$ ) and two sets of AB doublets [7.92, 8.21 ( $J=5\text{Hz}$ ) and 9.02, 9.38 ( $J=5\text{Hz}$ )]. Moreover, the elemental analysis of (37) supported the empirical formula  $\text{C}_{11}\text{N}_2\text{H}_6\text{O}_2$ . On this basis, (37) was assigned the structure of 2-hydroxy-7-oxo-1,6-diazaphenalene. In a similar fashion (4) was refluxed in excess trifluoroperacetic acid after which a brown solid (38) was obtained. The CI mass spectrum of this material had a parent ion at 231 ( $M^+ + 1$ ) while the infrared spectrum contained bands at 3240 (broad,  $\text{O}-\text{H}$  stretch), 1800 (strong), 1690 (s), 1445 (s), as well as the characteristic band of N-oxides at 1150-1300 (broad)  $\text{cm}^{-1}$ . Furthermore, the proton spectrum contained one singlet at  $\delta 8.16$  and two sets of AB doublets at 8.57, 8.81 ( $J=5\text{Hz}$ ) and 9.18, 9.45 ( $J=4\text{Hz}$ ), respectively. Chemical evidence for the structure of 38 was obtained by reduction of the N-oxide functions, according to the method of Yamanaka,<sup>26</sup>



to provide 37, 2-hydroxy-7-oxo-1,6-diazaphenalene.

SCHEME XI



### Acylation

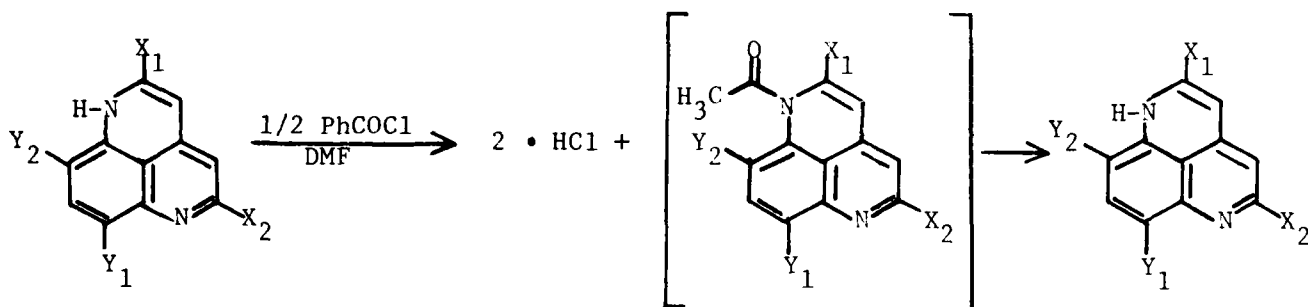
In order to protect the 7-amino-1,6-diazaphenalene species from oxidation it was felt, as mentioned previously that formation of 1-substituted diazaphenalenes might serve this purpose, therefore a program was begun designed to determine whether 4 could be acylated or alkylated at position -1. A simple examination of the structure of 4, as compared to that of imidazole, indicated that 4 might well behave in similar fashion,<sup>27</sup> consequently, acyl diazaphenalenes would be expected to be quite reactive toward nucleophiles.<sup>28</sup> With this hypothesis in mind, we set about to examine the reactivity of 1,6-diazaphenalene (4) and derivatives 39, 40, and 41 with acylating agents, moreover, the corresponding reactions with alkylating agents were also explored.

Although imidazoles are known to undergo N-acylation on heating in acetic anhydride,<sup>29</sup> none of the desired N-acylated products 42 or 43 were isolated when either 4 or 2,5-dichloro-1,6-diazaphenalene (39), respectively, were heated in this manner. It is believed that N-acetyl-1,6-diazaphenalene (42) had formed in the

reaction but the amide was too unstable to isolate for treatment of 2-chloro-9-methoxy-1,6-diazaphenalene (40) with hot acetic anhydride did provide the N-acyl derivative 44 which could be characterized as the amide. The appearance of a carbonyl band at  $1700\text{ cm}^{-1}$  in the infra red spectrum of 44 indicated the amide had formed and this was corroborated by the appearance of a singlet (3H) at  $2.54\delta$  in the proton NMR spectrum of this compound. Moreover, the base peak in the chemical ionization mass spectrum appeared at 275 mass units ( $P + 1$ , 100%) in complete agreement with the assigned structure. Facile loss of a fragment from the parent ion corresponding to the elements of  $\text{C}_2\text{H}_3\text{O}$  was also observed at 233 mass units. It is felt the 2-chloro and 9-methoxy groups of 44 flank the N-acyl function and inhibit the rapid hydrolysis of 44 to 40 rendering 44 isolable. This acyl-derivative 44, however, is quite labile for it reverts to 40 when subjected to column chromatography. The lack of stability of such amides was not surprising for N-acylimidazoles are known to rapidly undergo cleavage to imidazole when treated with nucleophiles.<sup>30</sup>

In 1962 Boyer reported that imidazole, when heated with isopropenyl acetate, was converted to N-acylimidazole in greater than 90% yield.<sup>31</sup> When 1,6-diazaphenalene 4 was heated in this reagent, tlc indicated the presence of three new compounds; however, only 1,6-diazaphenalene 4 could be isolated after workup. In contrast to the behavior of 4, the 2-chloro-9-methoxy derivative 40 was converted to the acyl diazaphenalene 44 when heated in isopropenyl acetate in agreement with earlier results with acetic anhydride described above.

SCHEME XII



41,  $X_1=X_2=Y_1=Y_2=\text{H}$

39,  $X_1=X_2=\text{Cl}$ ,  $Y_1=Y_2=\text{H}$

40,  $X_1=\text{Cl}$ ,  $X_2=\text{H}$ ,  $Y_1=\text{H}$ ,  $Y_2=\text{OCH}_3$

41,  $X_1=X_2=\text{Cl}$ ,  $Y_1=\text{NO}_2$ ,  $Y_2=\text{H}$

42,  $X_1=X_2=Y_1=Y_2$ , not observed

43,  $X_1=X_2=\text{Cl}$ ,  $Y_1=Y_2=\text{H}$ , not observed

44,  $X_1=\text{Cl}$ ,  $X_2=\text{H}$ ,  $Y_1=\text{H}$ ,  $Y_2=\text{OCH}_3$ , observed

45,  $X_1=X_2=\text{Cl}$ ,  $Y_1=\text{NO}_2$ ,  $Y_2=\text{H}$ , not observed

Indirect evidence also for the existence of acyl diazaphenalenes was observed when the most common method for preparation of N-acyl and N-aroyle imidazoles was attempted; treatment of two equivalents of imidazole with one equivalent of acyl or aroyle halide.<sup>32</sup> In this vein, two equivalents of 2,5-dichloro-1,6-diazaphenalene 39 were dissolved in scrupulously dried dimethyl formamide and reacted with one equivalent of benzoyl chloride. After a short while, a solid began to separate from the solution while tlc indicated the complete absence of starting 39. The solid (nearly one equivalent) which formed was filtered from the medium and was shown to be the hydrochloride salt of 39, which had also been prepared by an independent route. The filtrate, however, after careful removal of solvent, returned

only 39 and benzoic acid. It appears the desired N-benzoylation has taken place, but the reactive benzamide 43 (benzoyl instead of acetyl) was converted into 39 and the corresponding acid on exposure to moist air (see Scheme XII). Similar results were obtained with 4 and 41, and were also observed when acetyl and tosyl chlorides were substituted for benzoyl chloride.

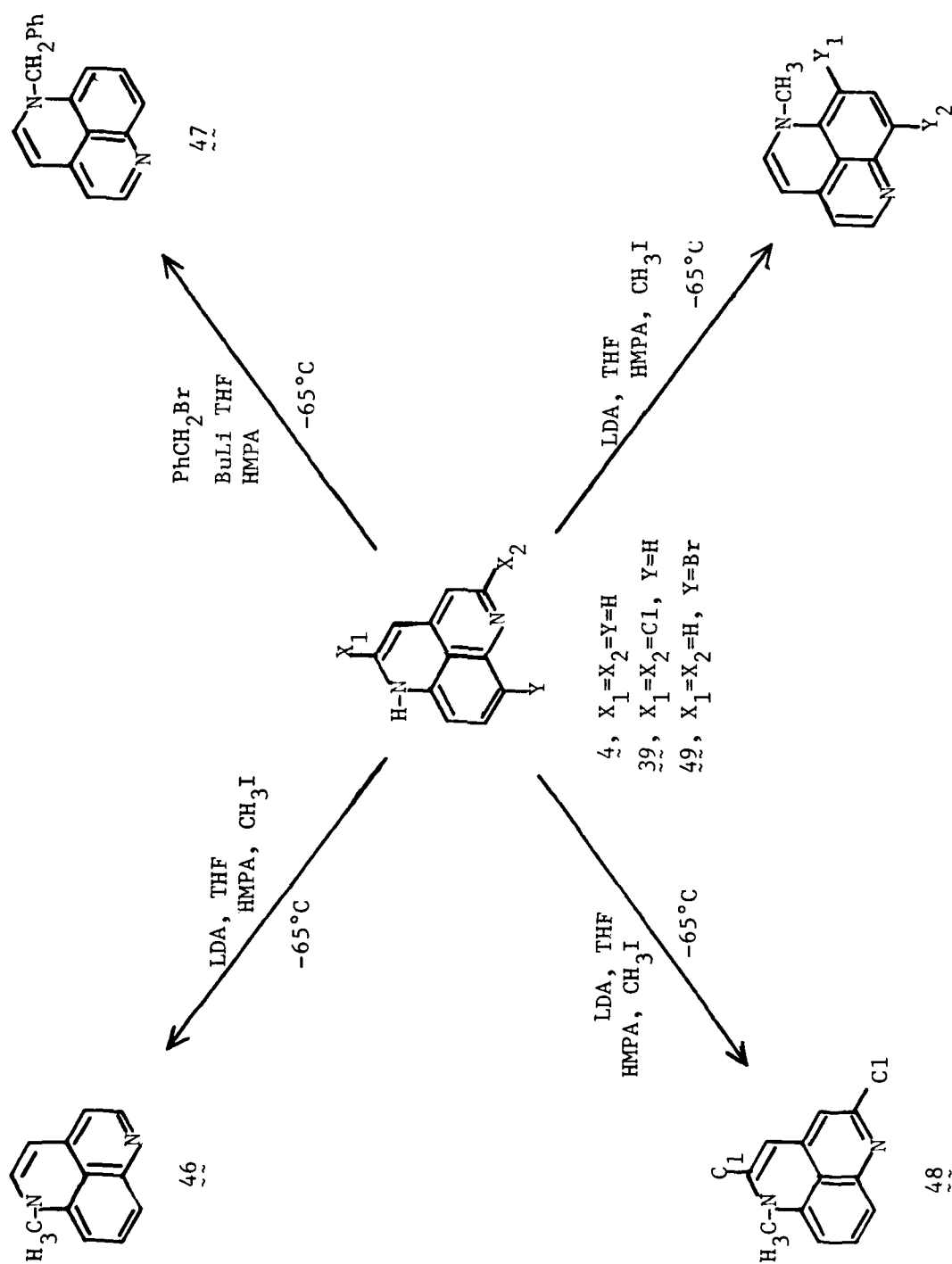
The existence of the N-acyl diazaphenylene 44 and the formation of 2,5-dichloro-1,6-diazaphenylene hydrochloride in better than 88% yield, coupled with the isolation of 39 and benzoic acid from the filtrate serve to indicate that the N-acyl intermediates are forming, but are generally too unstable to isolate. The lability of 44 to chromatography, in addition to the behavior of diazaphenylenes 4 and 41 toward acid halides also support this contention. It appears from this data that N-acyl-diazaphenylenes are then quite labile to hydrolysis as predicted.<sup>2a,b</sup>

### Alkylation

The presence of two different types of nitrogen atoms, in theory, in the skeleton of 1,6-diazaphenylene 1 increases the number of ways in which an N-substituted derivative can be prepared, analogous to the case for imidazoles. In fact, N-alkylation of imidazoles has been achieved under a myriad of conditions; for example, reaction of imidazole with one equivalent of an alkyl halide or sulfate in the presence of base effects N-alkylation in a straightforward manner.<sup>33</sup> In contrast, however, N-alkylation of the 1,6-diazaphenylene nucleus has proven to be much more difficult. Attempts to N-methylate 1,6-diazaphenylene (4) with dimethyl sulfate were not successful, furthermore 7-nitro-2,5-dichloro-1,6-diazaphenylene 41 when heated with either benzyl chloride or -bromide in xylene,<sup>34</sup> returned only starting nitro-diazaphenylene 41. Similarly, heating 1,6-diazaphenylene 4 with alkyl halides in the presence of potassium carbonate, analogous to the conditions employed for a similar alkylation of imidazole,<sup>35</sup> gave none of the N-alkylated product. Benzotriazole<sup>36</sup> and purines<sup>37</sup> can be N-alkylated with 2,3-dihydropyran; however, this method was ineffective when employed with a diazaphenylene such as 39, moreover heating 39 with ethylene carbonate<sup>38</sup> in refluxing xylene also gave no product of alkylation. In all of the alkylation attempts discussed above, nearly quantitative recovery of starting diazaphenylene was observed.

The failure of 1,6-diazaphenylene 1 to undergo N-alkylation under mild conditions was somewhat surprising for the pK<sub>a</sub> of 4, as indicated previously, is quite similar to that of imidazole. In the context of these observations, attention was now turned toward alkylation of diazaphenylene under more vigorous conditions; the use of organolithium bases. In this vein, 1,6-diazaphenylene 4 was treated with lithium diisopropylamide (THF/HMPA) at -65°, followed by addition of methyl iodide to provide good yields of N-methyl-1,6-diazaphenylene 46 (Scheme XIII). The hexamethyl phosphoramide cosolvent was necessary to solubilize the lithium stabilized anion of 4. The NMR spectrum of this base 46 was quite complex which reflected the fact that the pseudo plane of symmetry originally found in 4<sup>2a,b</sup> was no longer present in 46. The presence of a three-proton singlet at 3.05  $\delta$  indicated that N-alkylation had taken place in preference to alkylation on carbon, moreover, no N-H absorption was found on examination of the infra red spectrum of 46. As expected, N-methyl-1,6-diazaphenylene 46 melted at a lower temperature (104°C) than the parent 4 (228°C), again indicative of the absence of strong intermolecular hydrogen bonding in 46. In this same context, N-methyl-1,6-diazaphenylene 46 was readily soluble in chloroform, whereas 4 was much less soluble in this medium. The NMR and IR spectra of 46 coupled with the physical properties served to support the structure as assigned. Benzylation of 4 was also carried out, albeit in lower yield, by treatment of 1,6-diazaphenylene 4 with benzyl bromide and lithium diisopropylamide in hexamethyl phosphoramide to provide 47. Stirring 4, however, with n-butyl lithium at -65°, followed by addition of benzyl bromide provided the desired N-benzyl-1,6-diazaphenylene 47 in greater than 80% yield.

SCHEME XIII

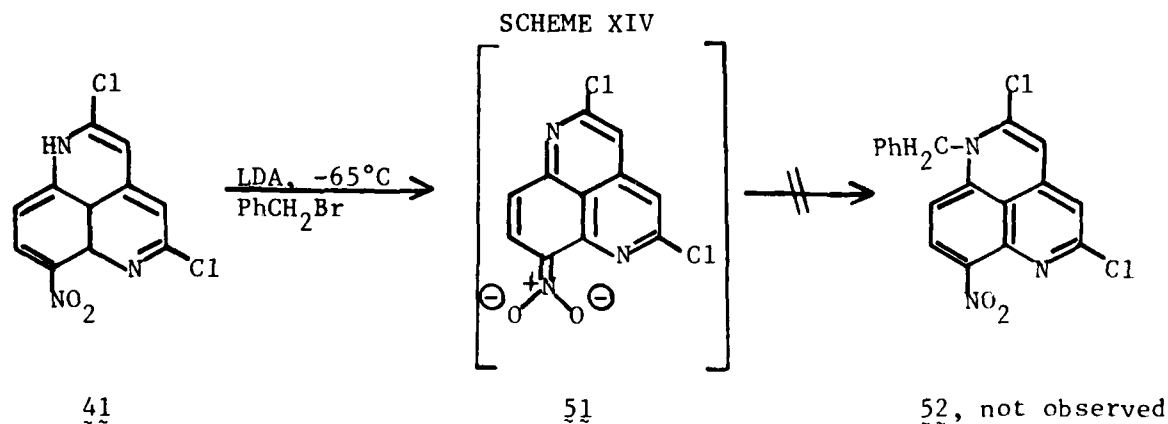


$50a$ ,  $Y_1 = H$ ,  $Y_2 = Br$   
 $50b$ ,  $Y_1 = Br$ ,  $Y_2 = H$

In a related set of experiments 2,5-dichloro-1,6-diazaphenalene 39 was treated with n-butyl lithium (HMPA/THF,  $-10^{\circ}\text{C}$ ), followed by addition of methyl iodide, which furnished a small amount of N-methyl-2,5-dichloro-1,6-diazaphenalene 48, in addition to small amounts of several other products. The NMR spectrum of 48 contained a three proton singlet at  $4.05\delta$  while the infra red spectrum was devoid of a band due to N-H absorption, moreover, the N-alkylated derivative 48 was quite soluble in chloroform, indicative again of the absence of intermolecular hydrogen bonding. Since metal-halogen exchange and aryne formation would be expected to result on treatment of 39 with n-butyl lithium, the base 39, was subsequently treated with lithium diisopropylamide at  $-65^{\circ}\text{C}$ , followed by addition of alkyl halide. This procedure suppressed the formation of by-products to provide 48 in better than 85% yield. While it is obvious that lithium diisopropylamide is the base of choice for these alkylations, it is believed the lower temperature ( $-65^{\circ}\text{C}$ ) is equally as important in this sequence for the prevention of aryne formation.

Since N-alkylation of an unsymmetrical 1,6-diazaphenalene could give rise to two different products (Scheme XIII) it became of interest to study the methylation of 7-bromo-1,6-diazaphenalene 49. In this experiment, 49 was reacted at  $-65^{\circ}\text{C}$  with methyl iodide, under conditions analogous to those reported for methylation of 4; furthermore, the N-methyl derivative 50 was isolated in better than 70% yield. No other alkylation products were found under these conditions. The spectral data (NMR, three proton singlet at  $4.95\delta$ ) are consistent with the alkylation of nitrogen; however, it is not clear at the moment whether the structure of the N-methyl-7-bromo-1,6-diazaphenalene is correctly represented by 50a or 50b.

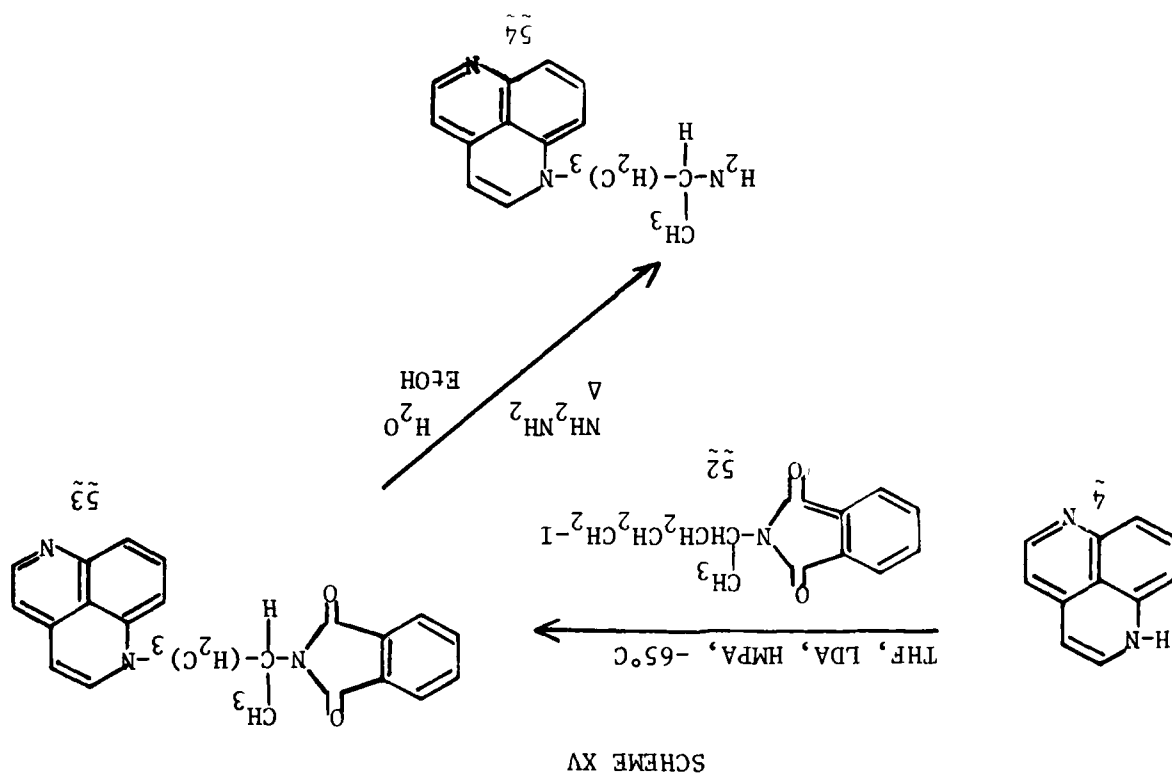
In contrast to the preparation of N-alkyldiazaphenalenenes substituted with hydrogen or halogen, the alkylation of diazaphenalenenes which carry a nitro substituent either does not occur or proceeds only sluggishly. For example, several attempts to form the N-benzyl derivative of 7-nitro-2,5-dichloro-1,6-diazaphenalene 41 in the presence of potassium carbonate or lithium diisopropylamide were not successful; quantitative recovery of 41 was realized in all cases. It is felt the negative charge originally on nitrogen is effectively delocalized onto the oxygen of the nitro group of 51 (Scheme XIV) which retards the reactivity of nitrogen toward electrophiles. The methylation of 7-nitro-1,6-diazaphenalene (11) has been carried out ( $\text{CH}_3\text{I}$ , lithium diisopropylamide, HMPA/THF), but the yield of alkylated product was less than 8%.<sup>39</sup> This and previous examples seem to support our contention that the 7-nitro-group is responsible for the lesser reactivity of the anion generated at position-1 of diazaphenalenenes.



The N-alkylation of 1,6-diazaphenalenenes which carry a variety of halo substituents can be readily accomplished using lithium diisopropylamide; however, diazaphenalenenes which are substituted at the seven position with a nitro group do not undergo this reaction as readily. Although alkylation reactions of 4 do not directly parallel similar transformations in the imidazole area, the formation of a labile N-acyl diazaphenalenene 44 is reminiscent of the reactivity of N-acylimidazoles.

#### Conclusion (Parent 1,6-Diazaphenalenene System)

The success of the alkylation reactions (LDA) presented above has resulted in the successful synthesis of target compound 54, the first in the 1,6-diazaphenalenene area (see Scheme XV). The alkyl iodide 52 was stirred with the lithium salt of the anion

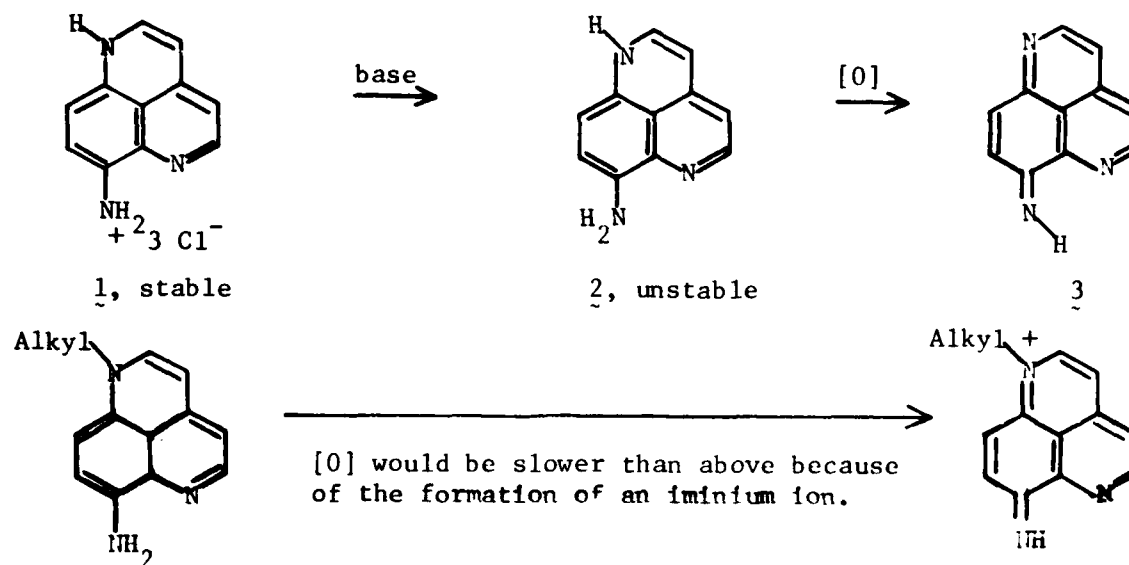


of 1,6-diazaphenalenene 4 to provide the N-alkylated phthalimido derivative 53 in 67% yield. This material was then converted to the target amine 54 on heating with hydrazine. This amine 54 was later converted to the dihydrochloride salt for transport to Walter Reed Army Research Institute. Although this compound is interesting, because it is related to a 5-aminoquinoline it lacks the 7-amino function necessary (we feel) for maximum activity (see below). At the outset of this report we indicated the need to find entries into stable 7-amino-1,6-diazaphenalenene targets as outlined in B.1. A summary of routes will now follow based on the chemistry of 1,6-diazaphenalenene 4 which addresses this point. One of the major aims was to synthesize molecules which would not undergo oxidation to the imine as rapidly as 2, consequently much work has been aimed

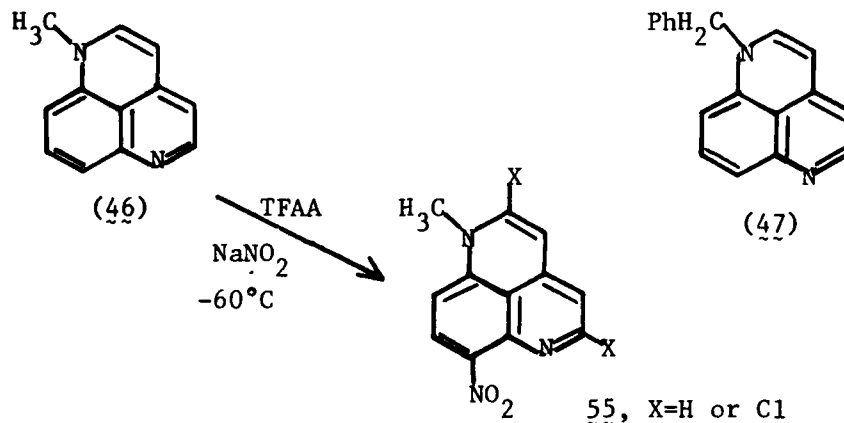


at preparation of N-substituted 1,6-diazaphenalenenes. This research has been suc-

# SCHEME XVI



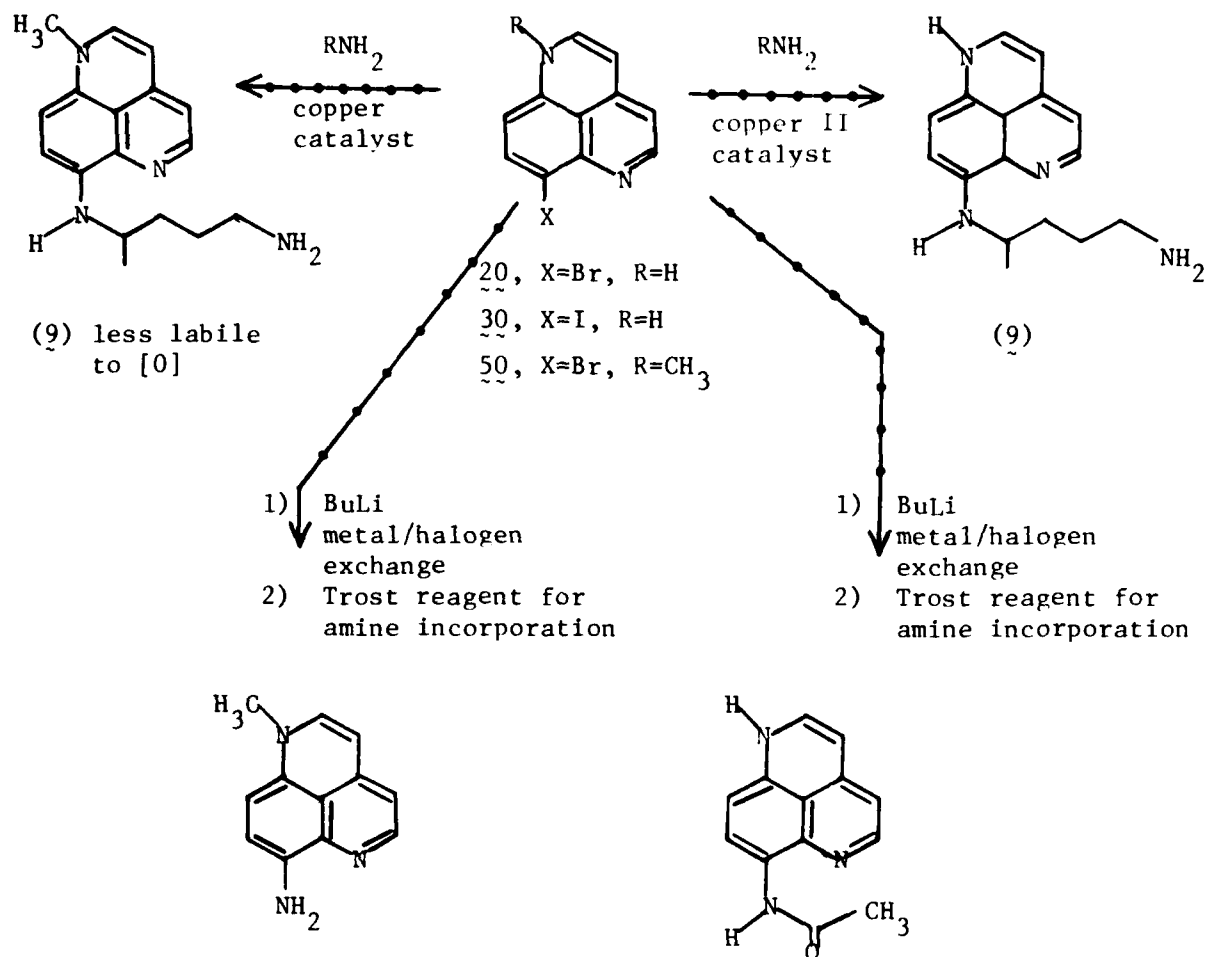
cussfully completed with the synthesis of N-methyl and also N-benzyl-1,6-diazaphenalenenes, illustrated below. In addition, employing the conditions of nitration worked out earlier,<sup>5</sup> the N-methyl analog has been converted to 1-methyl-7-nitro-



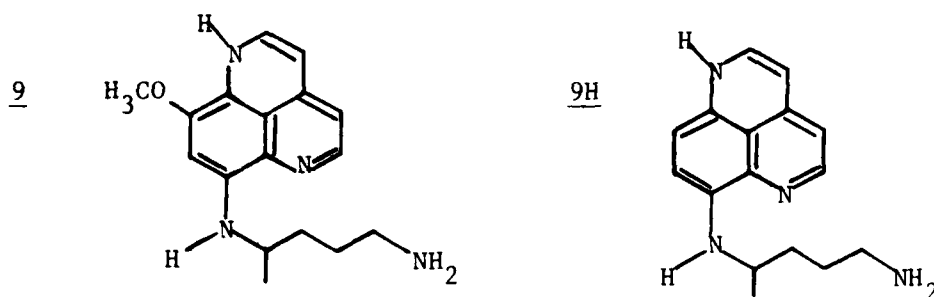
1,6-diazaphenalene (55). This material can now be reduced to the 1-methyl-7-amino analog and the stability of this 1,7-diamino-1,6-diazaphenalene studied. Once the sensitivity (to oxidation) of this compound is well-understood, targets (9) of the type illustrated in B.I. can be prepared. These are more likely to be active than 54 itself.

Since 8-haloquinolines can be coupled with amines to provide 8-aminoquinolines<sup>11</sup>, the successful preparation of 7-bromo-1,6-diazaphenalene (20), 7-iodo-1,6-diazaphenalene (30), and 1-methyl-7-bromo-1,6-diazaphenalene (50) provides yet another potential route to the targets of type (9). Extrapolation of the results reported in the 8-haloquinoline work to 7-halo diazaphenalenenes, as illustrated in Scheme XVII, should yield targets represented by (9). Furthermore, Trost and others have recently shown the aromatic anions can be made to add to amine acceptor molecules to provide substituted anilines. The halo derivatives 20, 30 and 40 would also serve as substrates for this approach to 7-amino-1,6-diazaphenalenenes.

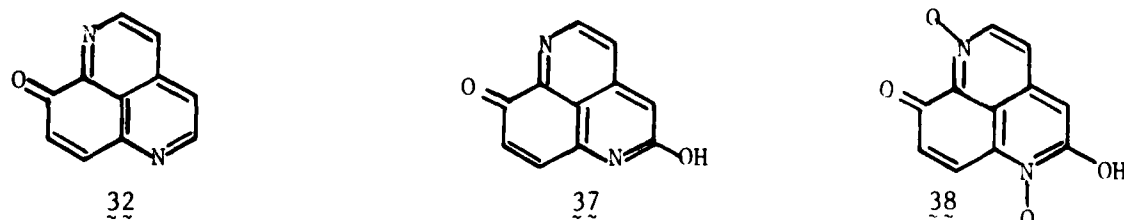
## SCHEME XVII



Finally in our previous proposal it was pointed out that 9-methoxy-1,6-diazaphenanthrene based antimalarials should be more active than their 9-H counterparts based on the activity of quinine (see, for example, 56). For this reason the product

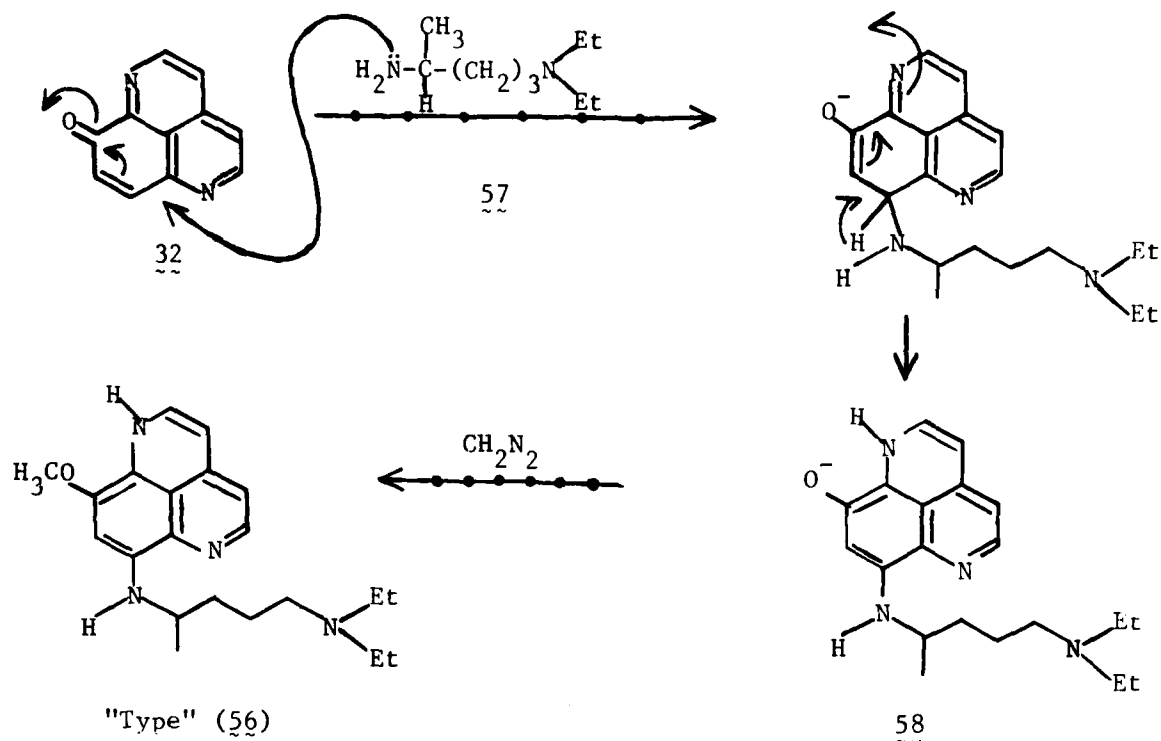


32, of the oxidation of 1,6-diazaphenanthrene with singlet oxygen, is of extreme interest.



The enone functionality present in **32** can be easily recognized as a potential Michael acceptor, consequently the nucleophilic addition of an alkylamine **57** to this enone is possible, as illustrated in Scheme XVIII. This would yield the desired target compound **56**, after treatment of the phenolic-like hydroxyl of **58** with diazomethane. In addition similar enones **37** and **38** can be prepared from

SCHEME XVIII



peracetic or pertrifluoroacetic acid oxidation of **4**.

The proposed routes represented above to targets such as (**9**) are different and distinct, yet have in common their origin from 1,6-diazaphenalene **4**. It is firmly believed the knowledge gained from the study of the chemistry of 1,6-diazaphenalene (**4**) will provide much easier and better routes to more stable target compounds than previously possible.

## EXPERIMENTAL

Microanalyses were performed on an F & M Scientific Corporation Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were carried out at the National Institutes of Health, Bethesda, Maryland. Melting points were taken on a Thomas Hoover melting point apparatus; they are uncorrected. Nuclear Magnetic Resonance spectra were recorded on Varian T-60, HA-100, and CFT-20 spectrometers while infrared spectra were recorded on a Beckman Acculab-1 instrument. Mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or Hewlett Packard 5855 GC/MS. High pressure liquid chromatography was performed on a Waters Preparative LC-500 Liquid Chromatograph. Analytical TLC plates employed in this work were Merck-Brinkmann UV active silica gel G on plastic.

7-Nitro-1,6-diazaphenalene (11). The 1,6-diazaphenalene [(4), 1.68 g, 0.01 mol] was suspended in dry chloroform (60 ml) with stirring, and trifluoroacetic acid (24.5 ml) was added until (4) completely dissolved. Sodium nitrite (0.69 g, 0.01 mol) was then added in small portions to the solution at  $-60^{\circ}\text{C}$  (chloroform/dry ice), after which the mixture was stirred for an additional 30 min at  $-60^{\circ}\text{C}$ . The solvent was removed under reduced pressure and the solid which remained was treated with aqueous ammonium hydroxide solution. A precipitate formed during this manipulation which was collected by filtration to furnish a red solid. The solid material was fractionated by column chromatography on alumina (tetrahydrofuran, benzene) to give 7-nitro-1,6-diazaphenalene [(11), 1.45 g, 68.08% yield] mp  $> 300^{\circ}\text{C}$ ; IR (KBr), 3160 (w), 1620 (s), 1600 (s), 1440 (s), 1220 (s), 1162 (s), 822 (s), 792 (s) and 731 (s)  $\text{cm}^{-1}$ ; NMR (trifluoroacetic acid)  $\delta$  7.27 (d, 1H,  $J=7\text{Hz}$ ), 7.29 (d, 1H,  $J=7\text{Hz}$ ), 7.58 (d, 1H,  $J=9\text{Hz}$ ), 8.20 (d, 1H,  $J=7\text{Hz}$ ), 8.42 (d, 1H,  $J=7\text{Hz}$ ) and 9.01 (d, 1H,  $J=9\text{Hz}$ ). 220 MHz NMR (trifluoroacetic acid)  $\delta$  7.27 (d, 1H,  $J=7\text{Hz}$ ), 7.29 (d, 1H,  $J=7\text{Hz}$ ), 7.58 (d, 1H,  $J=9\text{Hz}$ ), 8.20 (t, 1H,  $J=7\text{Hz}$ ), 8.42 (t, 1H,  $J=7\text{Hz}$ ) and 9.01 (d, 1H,  $J=9\text{Hz}$ ). CI mass spectrum ( $\text{CH}_4$ ) 214 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_7\text{N}_3\text{O}_2$ : C, 61.97; H, 3.31; N, 19.71. Found: C, 61.25; H, 3.25; N, 19.13.

Nitration of 1,6-Diazaphenalene (4) with Nitronium Tetrafluoroborate ( $\text{NO}_2\text{BF}_4$ )  
A slurry of 1,6-diazaphenalene [(4), 0.84 g, 0.005 mol] in dry tetrahydrofuran (80 ml) was treated in one portion with nitronium tetrafluoroborate (0.5 M 10, ml, 0.005 mol) in sulfolane, under nitrogen. The amber solution which resulted was stirred at room temperature for 1 h, and then concentrated under reduced pressure to furnish a thin oil. This oil was taken up in chloroform (80 ml) and washed with aqueous sodium bicarbonate solution (2.20 ml, 5%), followed later by water (20 ml). The organic layer was then dried oversodium sulfate. The solvent was removed under reduced pressure, the residue from which was chromatographed on silica gel (50 g, eluent - tetrahydrofuran). This provided an orange-red solid [(11), 0.51 g, 47.8% yield] which was identical in all respects to an authentic sample of 7-nitro-1,6-diazaphenalene (11) prepared in the previous reaction.

N-Methyl-7-nitro-1,6-diazaphenalene. To a stirred solution of lithium diisopropylamide (2 mmol,  $-65^{\circ}\text{C}$ ) in tetrahydrofuran [prepared by the addition of diisopropylamine (0.20 g, 2 mmol) to two equivalents of butyllithium under nitrogen] was added a solution of 7-nitro-1,6-diazaphenalene [(11), 0.19 g, 0.89 mmol] dissolved in a mixture of dry tetrahydrofuran (50 ml) and dry hexamethylphosphoramide (5 ml). The dark purple reaction mixture which resulted was stirred for 20 min at  $-65^{\circ}\text{C}$  followed by 15 min at room temperature. The reaction mixture was subsequently heated to reflux for 6 1/2 h, after which the solvent was removed under reduced pressure. Addition of water to the residue provided an orange-brown solid which was purified by careful column chromatography on alumina (eluent, tetrahydrofuran).

to provide the title compound [0.018 g, 8.91% yield] as an orange solid: mp 276-280°C; IR (KBr) 3086 (s), 3040 (w), 1630 (s), 1584 (s), 1480 (m), 1235 (s), 1142 (s), 835 (m), 738 (m); CI mass spectrum ( $\text{CH}_4$ ) 228 ( $M^+ + 1$ , 100%), NMR (trifluoroacetic acid) 7.20 (d, 1H,  $J=7\text{Hz}$ ), 7.26 (d, 1H,  $J=7\text{Hz}$ ), 7.40 (d, 1H,  $J=9.5\text{Hz}$ ), 8.18 (d, 1H,  $J=7\text{Hz}$ ), 8.28 (d, 1H,  $J=7\text{Hz}$ ) and 8.95 (d, 1H,  $J=9.5\text{Hz}$ ).

Reaction of (4) with Bromine/Acetic Acid [The Ratio of (4) to Sodium Acetate is 1:40]. The base, 1,6-diazaphenalene [(4), 1.0 g, 0.006 mol] was dissolved in acetic acid (anhydrous, 80 ml) and sodium acetate (20 g, 0.24 mol) was added with stirring. After (4) had completely dissolved, bromine (0.3 ml, 0.006 mol) was added dropwise. The solution at this point became cloudy and was stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure after which water was added to dissolve the sodium acetate which precipitated.

The product (0.84 g) which remained was a green solid composed of one major and two minor components, as indicated by TLC (silica gel, ethyl acetate). The products were separated by high pressure liquid chromatography (10% ethyl acetate/benzene). The first fraction provided 3,4,7-tribromo-1,6-diazaphenalene [(17), 0.256 g, 10.53% yield] as a green powder: mp > 300°C; IR (KBr) 3250 (s), 1584 (s), 1340 (s), 1262 (s), 1236 (s), 1178 (s), 1080 (m), 790 (m) and 684 (m)  $\text{cm}^{-1}$ ; NMR ( $\text{DMSO}-d_6$ )  $\delta$  6.20 (d, 1H,  $J=8\text{Hz}$ ), 7.42 (d, 1H,  $J=8\text{Hz}$ ), 7.88 (s, 1H), 8.26 (s, 1H); CI mass spectrum ( $\text{CH}_4$ ) m/e 406 ( $M^+ + 1$ , 100%), 326 (34).

Anal. Calcd for  $\text{C}_{11}\text{H}_5\text{N}_2\text{Br}_3$ : C, 32.63; H, 1.24, N, 6.92. Found: C, 32.49; H, 1.46; N, 7.01.

The two minor components were identified as 2,3,4-tribromo-1,6-diazaphenalene [(18), 0.151 g, 6.21% yield]: mp > 300°C, IR (KBr) 3325 (b), 1585 (s), 1340 (s), 1265 (s), 1235 (s), 790 (s), 765 (s), and 685 (s)  $\text{cm}^{-1}$ , NMR ( $\text{DMSO}-d_6$ )  $\delta$  6.22 (d, 1H,  $J=8\text{Hz}$ ), 7.40 (t, 1H,  $J=8\text{Hz}$ ), 7.58 (d, 1H,  $J=8\text{Hz}$ ) and 8.02 (s, 1H); CI mass spectrum ( $\text{CH}_4$ ) 406 ( $M^+ + 1$ , 32%).

Anal. Calcd for  $\text{C}_{11}\text{H}_5\text{N}_2\text{Br}_3$ : C, 32.63; H, 1.24; N, 6.92. Found: C, 32.98; H, 1.12; N, 7.03.

2,3-dibromo-1,6-diazaphenalene [(19), 0.100 g, 5.10% yield]: mp > 300°C; IR (KBr) 3065 (b), 1592 (s), 1338 (s), 1262 (s), 1239 (s), 804 (s), 785 (s), and 760 (s)  $\text{cm}^{-1}$ ; NMR (trifluoroacetic acid)  $\delta$  6.22 (d, 1H,  $J=7\text{Hz}$ ), 6.98 (d, 1H,  $J=9\text{Hz}$ ), 7.54 (t, 1H,  $J=7\text{Hz}$ ), 7.65 (d, 1H,  $J=7\text{Hz}$ ), and 8.14 (d, 1H,  $J=9\text{Hz}$ ); CI mass spectrum ( $\text{CH}_4$ ) 327 ( $M^+ + 1$ , 100%).

Anal. Calcd for  $\text{C}_{11}\text{H}_6\text{N}_2\text{Br}_2$ : C, 40.53; H, 1.86; N, 8.59. Found: C, 39.82; H, 2.01; N, 8.19.

In addition to the three bromo isomers above, unreacted [(4), 0.19 g, 0.001 mol] was also recovered.

Reaction of (4) with Bromine/Acetic Acid [The Ratio of (4) to Sodium Acetate was 1:24]. The diazaphenalene [(4), 1.68 g, 0.01 mol] was dissolved with sodium acetate (20 g, 0.24 mol) in glacial acetic acid (180 ml) with stirring. Bromine (0.51 ml, 0.01 mol), dissolved in acetic acid (anhydrous, 3.3 ml), was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure; the residue was washed with a small amount of water, dried overnight and yielded 0.998 g of crude product. TLC indicated the presence of one major and two minor components in the mixture. High pressure liquid chromatography (10% ethyl acetate/benzene) was employed to isolate 2,3,4-tribromo-1,6-diazaphenalene [(18), 0.323 g, 7.98% yield] as a pale green powder, its mp, IR, NMR and mass spectrum were also identical to (19) previously isolated. 7-Bromo-1,6-diazaphenalene [(20), 0.102 g, 4.16% yield]: mp > 300°C; IR (KBr) 2800 (b), 1850 (b), 1615 (s), 1565 (s), 1465 (s), 1322 (s), 1200 (s), 1100 (s), 862 (s) and 780 (s)  $\text{cm}^{-1}$ ; NMR ( $\text{DMSO}-d_6$ )  $\delta$  6.15 (1H, d,  $J=7\text{Hz}$ ), 6.35 (1H, d,  $J=5\text{Hz}$ ), 6.60 (1H, d,  $J=8\text{Hz}$ ), 7.40 (1H, d,  $J=7\text{Hz}$ ), 7.64 (1H, d,  $J=8\text{Hz}$ ) and 8.20 (1H, d,  $J=5\text{Hz}$ ); CI mass spectrum ( $\text{CH}_4$ ) 248 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_7\text{N}_2\text{Br}$ : C, 53.47; H, 2.86; N, 11.34. Found: C, 53.69; H, 2.72; N, 10.66.

Reaction of (4) with bromine/acetic acid [the ratio of (4) to sodium acetate was 1:24] at  $-10^{\circ}\text{C}$ . The diazaphenalene [(4), 1.68 g, 0.01 mol] was dissolved in glacial acetic acid (180 ml) and sodium acetate (20 g, 0.24 mol) was added to the mixture. Bromine (0.51 ml, 0.01 mol) was added dropwise to the solution at  $-10^{\circ}\text{C}$  (chloroform/dry ice), and the mixture stirred for 3 h. The solvent was removed under reduced pressure, after which the residue was left to dry overnight. TLC indicated the presence of one major and one minor component in the crude product. High pressure liquid chromatography (10% ethyl acetate/benzene) was employed to separate the compounds, and the first fraction provided 2,3,4-tribromo-1,6-diazaphenalene [(18), 0.084 g, 2.07% yield] as a pale green powder. The second fraction provided 2,3-dibromodiazaphenalene [(19), 0.385 g, 11.81% yield] as a yellowish-green powder, the mp, IR, NMR and mass spectra of both compounds were identical to those of (18) and (19), respectively, previously reported.

Reaction of (4) with One-half Equivalent of Bromine/Acetic Acid [the Ratio of (4) to Sodium Acetate was 1:24]. The heterocycle, 1,6-diazaphenalene [(4), 1.68 g, 0.01 mol] was dissolved with sodium acetate (20 g, 0.24 mol) in glacial acetic acid (180 ml) with stirring. Bromine (0.255 ml, 0.005 mol) was added dropwise after which the solution was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, then the residue was washed with water. The crude product was shown by TLC to contain one major and three minor components. Separation of the mixture by high pressure liquid chromatography (10% ethyl acetate/benzene) provided the major product, 3-bromo-1,6-diazaphenalene [(21), 0.282 g, 11.42% yield] as a green powder: mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 2860 (b), 1605 (s), 1550 (s), 1450 (s), 1283 (s), 1190 (s), 790 (s) and 760 (s)  $\text{cm}^{-1}$ ; NMR ( $\text{DMSO}-d_6$ )  $\delta$  5.83 (d, 1H,  $J=7\text{Hz}$ ), 6.72 (d, 1H,  $J=8\text{Hz}$ ), 7.00 (d, 1H,  $J=8\text{Hz}$ ), 7.36 (d, 1H,  $J=7\text{Hz}$ ), 7.41 (t, 1H,  $J=7\text{Hz}$ ) and 8.15 (s, 1H); CI mass spectrum ( $\text{CH}_4$ ) 248 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_7\text{N}_2\text{Br}$ : C, 53.47; H, 2.86; N, 11.34. Found: C, 52.86; H, 2.71; N, 11.20.

The three minor products were 7-bromo-1,6-diazaphenalene [(20), 0.189 g, 7.67% yield] accompanied by traces of 3,7-dibromo-1,6-diazaphenalene (22) and 2,3-dibromo-1,6-diazaphenalene (19); the mp, IR, NMR and mass spectral data for these three compounds were identical to those of (22) and (19), respectively, previously described.

Reaction of (4) with Bromine/Acetic Acid [the Ratio of (4) to Sodium Acetate was 1:1]. The diazaphenalene [(4), 1.68 g, 0.01 mol] was dissolved with sodium acetate (0.82 g, 0.01 mol) in glacial acetic acid (180 ml). After (4) dissolved, a solution of bromine (0.51 ml, 0.01 mol) was added dropwise in glacial acetic acid (4.4 ml). The solution was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was washed with water; examination by TLC indicated the presence of one major and three minor products. Separation of the mixture by high pressure liquid chromatography (10% ethyl acetate/benzene) furnished four pure components. The first fraction provided 2,3-dibromo-1,6-diazaphenalene [(19), 0.198 g, 6.07% yield] identical in all respects with a sample prepared previously. The second fraction gave 7-bromo-1,6-diazaphenalene [(20), 0.235 g, 9.51% yield]; the other product was 3-bromo-1,6-diazaphenalene [(21), 0.1 g, 4.05% yield]. These latter two compounds were also identical to (20) and (21) previously described. The last product was found to be 3,7-dibromo-1,6-diazaphenalene (22): mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 3050 (b), 1580 (s), 1320 (s), 1230 (s), 1162 (m), 1068 (m) and 750 (m)  $\text{cm}^{-1}$ ; NMR ( $\text{DMSO}-d_6$ )  $\delta$  6.42 (d, 1H,  $J=7\text{Hz}$ ), 7.21 (d, 1H,  $J=8\text{Hz}$ ), 7.55 (d, 1H,  $J=8\text{Hz}$ ), 8.04 (d, 1H,  $J=7\text{Hz}$ ) and 8.61 (s, 1H). CI mass spectrum ( $\text{CH}_4$ ) 327 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_6\text{N}_2\text{Br}_2$ : C, 40.53; H, 1.86; N, 8.59. Found: C, 40.82; H, 1.85; N, 7.93.

Reaction of (4) with Bromine/Trifluoroacetic Acid at  $-60^{\circ}\text{C}$ . The diazaphenalene [(4), 1.68 g, 0.01 mol] was suspended in dry methylene chloride (100 ml), after which trifluoroacetic acid (24.5 ml) was added until (4) went into solution. Bromine

(0.51 ml, 0.01 mol) was then dissolved in methylene chloride solution (50 ml) and added dropwise to the solution at  $-60^{\circ}\text{C}$  (chloroform/dry ice). The mixture was held at  $-60^{\circ}\text{C}$  for 1 h and then brought to room temperature after which it was allowed to stir an additional 30 min. The solvent was removed under reduced pressure after which potassium hydroxide solution (saturated) was added to neutralize the trifluoroacetic acid. At this point, an orange colored compound precipitated from the solution. This material was filtered and washed with a small amount of water and left to dry overnight. TLC indicated the presence of one major and one minor product (<10%). Column chromatography on alumina (tetrahydrofuran, ethyl acetate) yielded 7-bromo-1,6-diazaphenalene [(20), 2 g, 80.97% yield]. This compound was identical to (20), previously prepared, based on comparison of the mp, IR, NMR and mass spectral data obtained on an authentic sample of (20).

Reaction of (4) with Bromine/Trifluoroacetic Acid at Room Temperature. The diazaphenalene [(4), 1.68 g, 0.01 mol] was suspended in dry methylene chloride (100 ml), after which trifluoroacetic acid (24.5 ml) was added until (4) went into solution. Bromine (0.51 ml, 0.01 mol) was then dissolved in methylene chloride (50 ml) and added dropwise to the solution at room temperature. The solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure after which potassium hydroxide solution (saturated) was added to neutralize the trifluoroacetic acid. At this point, a green colored compound precipitated from the solution. This material was filtered and washed with a small amount of water and left to dry overnight; TLC indicated the presence of two products. Column chromatography (silica gel, tetrahydrofuran/ethyl acetate) was employed to separate the major 7-bromodiazaphenalene [(20), ~70% yield] from the minor product, 2,3-dibromodiazaphenalene (19), the mp, IR, NMR and mass spectral data for 19 and 20 have been reported above.

Bromination of 1,6-Diazaphenalene (4) with N-Bromosuccinimide (NBS). The diazaphenalene [(4), 0.84 g, 0.005 mol] was suspended in dry methylene chloride (50 ml), and trifluoroacetic acid (5 ml) was added until (4) completely dissolved. N-Bromosuccinimide (0.89 g, 0.005 mol) was then added in small portions and the solution allowed to stir at room temperature for 30 min. The solvent was removed under reduced pressure, after which sodium carbonate solution (saturated) was added to bring the pH above 7. A yellow compound precipitated during this process which was filtered and washed with water. The crude product was left to dry overnight. Examination of the solid on TLC indicated one major product was present which was purified by column chromatography on alumina (tetrahydrofuran, ethyl acetate) to yield 7-bromo-1,6-diazaphenalene [(20), 0.8 g, 64.78% yield].

Reaction of 1,6-Diazaphenalene (4) with N-Chlorosuccinimide. The 1,6-diazaphenalene [(4), 0.84 g, 0.005 mol] was suspended in dry methylene chloride (50 ml), followed by addition of trifluoroacetic acid (5 ml). N-Chlorosuccinimide (0.668 g, 0.005 mol) was added portionwise to the solution, with stirring, at room temperature. After 1 h, the solvent was removed from the reaction mixture under reduced pressure, after which the residue was washed with aqueous sodium carbonate solution. This treatment provided a yellow-brown solid (1.0 g) which was composed of four components by TLC. Separation of the mixture by high pressure liquid chromatography (10% tetrahydrofuran/benzene) yielded the compounds described below: 2,3-dichloro-1,6-diazaphenalene [(27), 0.137 g, 11.56% yield]: mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 2650 (b), 1600 (s), 1562 (s), 1470 (s), 1340 (s), 1252 (s), 1080 (s), 1010 (s) and 785 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$  6.22 (d, 1H, J=7Hz), 6.98 (d, 1H, J=9Hz), 7.54 (t, 1H, J=7Hz), 7.65 (d, 1H, J=7Hz) and 8.14 (d, 1H, J=9Hz); CI mass spectrum 237 ( $M^{+}+1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_6\text{N}_2\text{Cl}_2$ : C, 55.73; H, 2.55; N, 11.82. Found: C, 55.22; H, 2.40; N, 11.12.

7-Chloro-1,6-diazaphenalene [(25), 0.34 g, 33.57% yield]: mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 2800 (b), 1700 (s), 1600 (s), 1562 (s), 1468 (s), 1335 (s), 1278 (s), 1180 (s) and 795 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$  5.98 (d, 1H, J=6.5Hz), 6.21 (d, 1H, J=5Hz), 6.60 (d, 1H,

$J=7.5\text{Hz}$ ), 6.87 (d, 1H,  $J=6.5\text{Hz}$ ), 7.41 (d, 1H,  $H=7.5\text{Hz}$ ) and 7.82 (d, 1H,  $J=5\text{Hz}$ ); CI mass spectrum 203 ( $M^++1$ , 100%).

Anal. Calcd. for  $C_{11}H_7N_2Cl$ : C, 65.20; H, 3.48; N, 13.82. Found: C, 65.05; H, 3.79; N, 13.67.

3,7-Dichloro-1,6-diazaphenalene [(28), 0.093 g, 7.86% yield], mp  $> 300^\circ\text{C}$ ; IR (KBr) 2950 (b), 1615 (s), 1570 (s), 1540 (s), 1465 (m), 1422 (m), 1328 (s), 1250 (s), 1090 (s), 1020 (s) and 785 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 5.94 (d, 1H,  $J=7\text{Hz}$ ), 6.70 (d, 1H,  $J=8\text{Hz}$ ), 7.02 (d, 1H,  $J=8\text{Hz}$ ), 7.48 (d, 1H,  $J=7\text{Hz}$ ) and 8.18 (s, 1H); CI mass spectrum 237 ( $M^++1$ , 100%).

Anal. Calcd. for  $C_{11}H_7N_2Cl$ : C, 65.20; H, 3.48; N, 13.82. Found: C, 65.73; H, 3.75; N, 13.26.

3-Chloro-1,6-diazaphenalene (26); NMR (DMSO- $d_6$ )  $\delta$ 5.79 (1H, d,  $J=7\text{Hz}$ ) 6.60 (1H, d,  $J=8\text{Hz}$ ), 6.95 (1H, d,  $J=8\text{Hz}$ ), 7.29 (1H, d,  $J=7\text{Hz}$ ), 7.34 (1H, t,  $J=8\text{Hz}$ ) and 8.03 (1H, s). Mass spectrum CI ( $\text{CH}_4$ ) 203 ( $M^++1$ ).

Reaction of 1,6-Diazaphenalene (4) with N-Iodosuccinimide. The 1,6-diazaphenalene [(4), 0.84 g, 0.005 mol] was suspended in methylene chloride (50 ml) followed by addition of trifluoroacetic acid (5 ml) until (4) had completely dissolved. N-Iodosuccinimide (1.125 g, 0.005 mol) was then added portionwise to the solution, with stirring, at room temperature. After stirring for 1 h at room temperature, the solvent was removed from the solution under reduced pressure. The solid which remained was washed with aqueous sodium carbonate which provided a yellow-brown solid (2.04 g). This material was purified by column chromatography (silica gel; tetrahydrofuran, ethyl acetate) to provide 7-iodo-1,6-diazaphenalene [(30), 0.671 g, 45.65% yield]: mp  $> 300^\circ\text{C}$ ; IR (KBr) 2920 (b), 1590 (s), 1550 (s), 1450 (m), 1420 (m), 1310 (s), 1270 (s), 1190 (m), 1095 (m) and 780 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 5.98 (d, 1H,  $J=7\text{Hz}$ ), 6.32 (d, 1H,  $J=5\text{Hz}$ ), 6.43 (d, 1H,  $J=8\text{Hz}$ ), 7.22 (d, 1H,  $J=7\text{Hz}$ ), 7.81 (d, 1H,  $J=8\text{Hz}$ ), and 8.06 (d, 1H,  $J=5\text{Hz}$ ); CI mass spectrum 295 ( $M^++1$ , 100%).

Anal. Calcd. for  $C_{11}H_7N_2I$ : C, 44.93; H, 2.40; N, 9.53. Found: C, 45.02; H, 2.78; N, 9.64.

7-Phenyl( $d_5$ )azo-1,6-diazaphenalene (15- $d_5$ ). Aniline- $d_5$  (0.491 g, 0.005 mol) was dissolved in hydrochloric acid (10 ml), and was subsequently treated with sodium nitrite (0.345 g, 0.005 mol in 3 ml of water) with chilling. A solution of 1,6-diazaphenalene [(4), 0.84 g, 0.005 mol] in acetic acid (6 ml) was diluted with water (20 ml). The solution was chilled to  $-10^\circ\text{C}$ , and the solution of phenyldiazaonium chloride- $d_5$  was slowly added with stirring. After the reaction was allowed to stir at  $-10^\circ\text{C}$  for 45 min, the mixture was made alkaline with ammonium hydroxide. The brown precipitate which formed was filtered from the mixture and subsequently washed with water. A red-purple solid was isolated from the precipitate by column chromatography (silica gel; tetrahydrofuran, benzene) which was identified as the 7-phenyl-azo derivative (15- $d_5$ ): mp  $> 300^\circ\text{C}$ ; IR (KBr) 2900 (s), 1570 (s), 1500 (s), 1415 (s), 1340 (m), 1186 (s), 1080 (s) and 760 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 6.50 (d, 1H,  $J=7\text{Hz}$ ), 6.82 (d, 1H,  $J=7\text{Hz}$ ), 7.27 (d, 1H,  $J=8\text{Hz}$ ), 7.58 (d, 1H,  $J=8\text{Hz}$ ), 8.10 (d, 1H,  $J=7\text{Hz}$ ) and 8.52 (d, 1H,  $J=7\text{Hz}$ ); CI mass spectrum 278 ( $M^++1$ , 100%).

Anal. Calcd. for  $C_{17}H_7N_4D_5$ : C, 73.62; H, 2.54; N, 20.20. Found: C, 73.53; H, 2.76; N, 19.89.

2-Hydroxy-7-oxo-1,6-diazaphenalene-1,6-dioxide (38). Trifluoroacetic acid solution for this experiment was prepared<sup>24</sup> by the dropwise addition of 30% hydrogen peroxide (5.0 ml, 44 mmol) to trifluoroacetic acid (37.50 ml) at  $0^\circ\text{C}$  (ice bath). The ice bath was then removed, and 1,6-diazaphenalene [(4), 0.42 g, 0.0025 mol] added slowly after which the solution was held at reflux for 2 h. During this period the deep green solution became bright red. The solvent was removed under reduced pressure, and the residue was brought to alkaline pH with aqueous sodium carbonate solution (saturated). This yielded a yellow precipitate which was filtered from the



medium and left overnight to dry. This material was purified by passing through a short column of silica gel (eluent, tetrahydrofuran) to provide [(38), 0.08 g, 6.98% yield] as a brown solid: mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 3240 (b), 2380 (b), 1800 (s), 1690 (s), 1445 (s), 1150-1300, and 780 (b)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 8.16 (s, 1H), 8.52 (d, 1H,  $J=5\text{Hz}$ ), 8.81 (d, 1H,  $J=5\text{Hz}$ ), 9.18 (d, 1H,  $J=5\text{Hz}$ ) and 9.45 (d, 1H,  $J=5\text{Hz}$ ); CI mass spectrum 231 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{N}_2\text{O}_4\text{H}_6$ : C, 57.40; H, 2.63; N, 12.17. Found: C, 57.72; H, 2.59; N, 11.89.

2-Hydroxy-7-oxo-1,6-diazaphenalene (37). The 1,6-diazaphenalene [(4), 0.42 g, 0.0025 mol] was dissolved in glacial acetic acid (30 ml) and hydrogen peroxide (30%, 1.05 ml, 0.01 mol) was added dropwise to the solution, after which the green colored solution became dark red. The mixture was allowed to reflux for 2 h, followed by removal of the solvent under reduced pressure. The residue was washed with saturated sodium carbonate solution to provide the crude product (0.168 g). This solid was purified by column chromatography on silica gel (tetrahydrofuran) to give [(37), 0.105 g, 10.61% yield] as a red solid: mp  $> 300^{\circ}\text{C}$ ; IR (KBr) 2875 (s), 1680 (s), 1460 (s), 1345 (s), 1220 (s), 760 (s) and 665 (s)  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 7.00 (s, 1H), 7.92 (d, 1H,  $J=5\text{Hz}$ ), 8.21 (d, 1H,  $J=5\text{Hz}$ ), 9.02 (d, 1H,  $J=4\text{Hz}$ ) and 9.38 (d, 1H,  $J=4\text{Hz}$ ); CI mass spectrum ( $\text{NH}_3$ ) 199 ( $M^+ + 1$ , 100%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_6\text{N}_2\text{O}_2$ : C, 66.67; H, 3.05; N, 14.14. Found: C, 66.97; H, 3.12; N, 14.41.

2,3-Dihydro-1,6-diazaphenalene. A sample of 2,5-dichloro-1,6-diazaphenalene [(39), 7.0 g, 0.03 mol] was dissolved in absolute ethanol (300 ml), followed by addition of palladium on carbon (5%, 2.5 g) to the solution. Hydrazine hydrate (50 ml of 95% hydrazine hydrate) taken up in ethanol (50 ml) was added to the mixture at reflux. The reaction mixture was allowed to reflux for 5 h after which another portion of hydrazine hydrate (10 ml hydrazine and 10 ml ethanol) was added. The solution was held at reflux for another 10 h. The catalyst was then removed by filtration and the solvent removed under reduced pressure. Water (5 ml) was added to the residue after which the brightly colored orange-yellow solid which resulted was filtered from the solution. The solid was washed once with a saturated aqueous solution of sodium bicarbonate to give a mixture (4.4 g) of two products. This material was separated by column chromatography on alumina (tetrahydrofuran). The least polar compound 2,3-dihydro-1,6-diazaphenalene [0.47 g] was obtained as a pale yellow solid: mp  $128^{\circ}\text{C}$ ; IR (KBr) 3240, 3120, 2960, 2822, 1620, 1590, 1510, 1410, 1230, 1130, 1080, 840 and 740  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$ 2.9-3.6 (m, 4H), 4.67 (broad, 1H, NH), 6.53 (t, 1H,  $J=6\text{Hz}$ ), 6.9 (d, 1H,  $J=6\text{Hz}$ ), 7.4 (d, 2H,  $J=6\text{Hz}$ ) and 8.97 (d, 1H,  $J=6\text{Hz}$ ); CI mass spectra ( $\text{CH}_4$ ) 171 ( $M^+ + 1$ , 100%) 170 (26%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2$ : C, 77.62; N, 5.92; H, 16.46. Found: C, 77.56; H, 6.02; N, 16.38.

The more polar compound was found to be 4 present in greater than 70% yield.

Attempted Oxidation of 1,6-Diazaphenalene (4) with 30% Sulfuric Acid/Potassium Dichromate and 75% Sulfuric Acid/Potassium Dichromate. The 1,6-diazaphenalene [(4), 0.168 g, 0.001 mol] was dissolved in sulfuric acid (30%, 10 ml) in an ice bath. After (4) dissolved, potassium dichromate (0.049 g, 0.167 mmol) was added in small portions, and the resulting mixture allowed to stir at room temperature for 18 h. After this period, aqueous potassium hydroxide was added to neutralize the solution upon which a green precipitate deposited on the walls of the flask. This material was filtered from the mother liquor and left to dry overnight to provide 0.095 grams of a solid. This precipitate was shown by spectroscopy to be identical in all respects with starting (4). When 75% sulfuric acid was used in place of 30% sulfuric acid (4) decomposition took place, and black amorphous material was obtained.

Attempted Oxidation of 1,6-Diazaphenalene with m-Chloroperbenzoic Acid. A suspension of 1,6-diazaphenalene (0.42 g, 0.0025 mol) in acetic acid (anhydrous, 20 ml) which contained m-chloroperbenzoic acid (0.8625 g) was stirred at reflux for 3 h. Acetic acid was subsequently removed under reduced pressure and the residue was stirred with ether (40 ml), followed by filtration. The solid which remained was extracted with tetrahydrofuran and subjected to column chromatography (silica gel, tetrahydrofuran). This procedure yielded two compounds which proved to be the starting material, 1,6-diazaphenalene (4), and m-chlorobenzoic acid.

Nitration of N-Methyl-2,5-Dichloro-1,6-Diazaphenalene at -60°C. To a cooled solution (-60°C) of 1-methyl-2,5-dichloro-1,6-diazaphenalene (0.92 g, 3.66 mmol) in chloroform (100 ml) and trifluoroacetic acid (10 ml) was added sodium nitrite (0.27 g, 3.91 mmol) in one portion. The reaction mixture was stirred below -60°C for 1 h and then allowed to stir at room temperature for 18 hr. Methanol was then added to the reaction mixture and the solvents were subsequently removed under reduced pressure to provide a dark oil (1.3 g). This material was purified by column chromatography on alumina (10% ethyl acetate/benzene). The overall yield of this sequence was 93% of which 0.13 grams (12.87%) were composed of 1-methyl-2,5-dichloro-7(9)-nitro-1,6-diazaphenalene (mp 223-25°C), 0.48 grams (47.52%) were 1-methyl-2,5-dichloro-3(4)-nitro-1,6-diazaphenalene and finally 0.40 grams (39.6%) were found to be 1-methyl-2,5-dichloro-9(7)-nitro-1,6-diazaphenalene: mp 223-225°C; IR (KBr) 3095 (10), 2965 (w), 1615 (s), 1582 (s), 1479 (s), 1230 (s), 1060 (s), 878 (m), 734 (m); NMR (CF<sub>3</sub>COOH)  $\delta$ 3.89 (3H, s), 7.10 (1H, s), 7.29 (1H, s), 7.60 (1H, d, J=9Hz), 8.56 (1H, d, J=9Hz). CI mass spectrum (CH<sub>4</sub>), 296.0 (M<sup>+</sup>+1, 100%). 1-methyl-2,5-dichloro-3(4)-nitro-1,6-diazaphenalene: mp 282-284°C; IR (KBr) 3122 (w), 3048 (w), 1614 (s), 1580 (s), 1488 (s), 1288 (m), 1138 (s), 865 (m), 720 (m); NMR (CF<sub>3</sub>COOH)  $\delta$ 4.33 (3H, s), 7.42 (1H, s), 7.56-7.87 (2H two unresolved doublets, J=8Hz), 8.24 (1H, dd, J<sub>1</sub>=J<sub>2</sub>=8Hz). CI mass spectrum (CH<sub>4</sub>) 296.0 (M<sup>+</sup>+1, 100%). 1-methyl-2,5-dichloro-9(7)-nitro-1,6-diazaphenalene: mp 246-250°C; IR (KBr) 1620(s), 1580(s), 1298 (s) 870 (m); NMR (CF<sub>3</sub>COOH)  $\delta$ 4.39 (3H, s), 7.30 (1H, s), 7.45 (1H, s), 7.75 (1H, d, J=9Hz), 9.16 (1H, d, J=9Hz). CI mass spectrum (CH<sub>4</sub>), 296.0 (M<sup>+</sup>+1, 100%).

Attempted Reaction of 39 with Dihydropyran. A suspension of 39 (0.7 g, 2.95 mmol) and p-toluene sulfonic acid (catalytic amount) in ethyl acetate was heated to reflux, and 2,3-dihydropyran (0.25 g, 2.97 mmol) was added. The mixture was heated for 72 hr at which time TLC indicated only the presence of 39. Starting 3 was recovered in near quantitative yield.

Attempted Alkylation of 7-Nitro-2,5-Dichloro-1,6-Diazaphenalene (41) with Dimethyl Sulfate. A slight excess of dimethyl sulfate was added at room temperature to a turbid solution of 41 in dimethyl formamide in the presence of aqueous sodium hydroxide (2N, 2 equivalents) solution. The mixture was stirred at room temperature for 1 h, after which TLC indicated the presence of starting 41. The solution was then heated to reflux for one half hour after which an orange solid began to precipitate from solution. This solid which was shown to be starting 41 was recovered in greater than 90% yield.

Attempted Benzylation of 7-Nitro-2,5-Dichloro-1,6-Diazaphenalene (41). A mixture of 41 and excess benzyl chloride (or bromide) was heated in xylene for 94 hr both in the presence and absence of potassium carbonate. At no time was any of the alkylated product observed on TLC, and starting 41 was recovered in greater than 95% yield.

Preparation of 1-Acetyl-2-Chloro-9-Methoxy-1,6-Diazaphenalene (44). A sample of 2-chloro-9-methoxy-1,6-diazaphenalene (40, 0.52 g, 2.1 mmol) prepared by the method of Weber<sup>40</sup> was heated for 3 h in refluxing acetic anhydride (5 ml). The solu-

tion was then cooled and poured into cold water after which the pH was brought to neutral on addition of cold aqueous ammonium hydroxide (14%). A solid precipitated from the solution, and was collected by filtration to give the title compound 44 (0.47 g, 82% yield): mp 164-166°C; IR (KBr) 1700, 1640, 1290 and 1230  $\text{cm}^{-1}$ ; NMR (DMSO- $d_6$ )  $\delta$ 2.54 (3H, s), 3.93 (3H, s), 6.78 (1H, d,  $J=8\text{Hz}$ ), 6.92 (1H, s), 7.23 (1H, d,  $J=9\text{Hz}$ ), 7.61 (1H, d,  $J=8\text{Hz}$ ) and 8.48 (1H, d,  $J=9\text{Hz}$ ); mass spectrum (CI,  $\text{CH}_4$ ), 275 (P+1, 100%).

This material was stable in a dessicator for several months as a solid; however, on chromatography it decomposed to return 40.

Reaction of 40 with Isopropenylacetate to Provide 44. A suspension of 40 (170 mg, 0.73 mmol) was heated in isopropenyl acetate (10 ml) for 24 hr.<sup>31</sup> The reaction mixture was cooled and filtered to remove undissolved solids (70 mg). The filtrate was concentrated under reduced pressure to provide a solid (88 mg) which was identical to 1-acetyl-2-chloro-9-methoxy-1,6-diazaphenalene (44): mp 164-166°C; IR (KBr) 1700  $\text{cm}^{-1}$  (C=O); mass spectrum (C.I.,  $\text{CH}_4$ ), 275 (P+1, 23%), 233 (100%), TLC ( $R_f$  value identical to the  $R_f$  of authentic 44). Thin layer chromatography also indicated the presence of a small amount of starting 40 in this solid; however, it is believed this phenomenon was due to the degradation of 44 on the silica gel TLC plate.

When the same sequence was carried out with 1,6-diazaphenalene 4 in place of 40, three new compounds were observed on TLC; however, at no time were we able to isolate the acetamide derivative 42. On several occasions it appeared (NMR and IR spectroscopy) that a mixture of 4 and acetic acid had been produced, for treatment of the solid with sodium bicarbonate solution or water did regenerate 4.

Attempted Acetylation of 2,5-Dichloro-1,6-Diazaphenalene (39) with Acetic Anhydride. A suspension of 39 was heated in refluxing acetic anhydride for 90 min. analogous to the conversion of 40 to 44 in the same reagent previously discussed. Soon after the mixture was brought to reflux the solid dissolved; however, by the end of the 90 min. period a small amount of dark black material had precipitated. This was filtered from the reaction mixture and water was added to the filtrate. The solid which precipitated from the filtrate was identified as starting material 39, recovered in better than 90% yield.

When this sequence was repeated, and the solution was held at reflux for extended periods of time (40 hrs), polymeric material resulted.

Reaction of 2,5-Dichloro-1,6-Diazaphenalene (39) with p-Toluene Sulfonyl Chloride. A solution of (39, 0.956 g, 4.0 mmol) and p-toluene sulfonyl chloride (0.382 g, 2.0 mmol) in dry dimethylformamide was stirred at room temperature for 18 h. After several hours, a yellow-orange solid precipitated from the solution which was identified as the salt, 2,5-dichloro-1,6-diazaphenalene hydrochloride (0.44 g). A portion (1 ml) of the supernatant liquid was added to water and the solid which resulted was dried. This solid was shown to be 39 for no depression of the melting point was observed on admixture with authentic 39.

The remainder of the supernatant liquid from above was concentrated under reduced pressure to provide a dark colored sticky solid. This material was subjected directly to mass spectrometry, however, no ion consistent with the desired sulfonamide could be found in the spectrum. Nevertheless, on treatment with base this sticky solid returned 39. The total recovery of 39 from this experiment was greater than 90%.

Reaction of 2,5-Dichloro-1,6-Diazaphenalene (39) with Benzoyl Chloride. A mixture of (39, 0.712 g, 3.0 mmol) and benzoyl chloride (0.21 g, 1.5 mmol) was dissolved in dry dimethylformamide and stirred for 3 h. At this time, TLC indicated the absence of starting material and the appearance of a more polar compound was observed. A yellow-green solid (220 mg) separated from the solution during this

period, and was found to be 2,5-dichloro-1,6-diazaphenalene hydrochloride while another crop of crystals (120 mg) precipitated on stirring an additional four hours (total wt, 0.34 g; 82.93% of expected 39 hydrochloride).

A portion of the filtrate (1 ml) was added to water which immediately provided a yellow solid identical in spectral properties with those obtained previously for 39. The remainder of the filtrate was concentrated under reduced pressure to furnish a sticky solid during which time a white solid also deposited on the neck of the flask. The infra red spectrum and melting point of this white solid were identical to those of an authentic sample of benzoic acid. The oily residue which remained was subjected to mass spectroscopy; however, no ion corresponding to the desired benzamide derivative of 39 was observed.

1-Methyl-1,6-diazaphenalene (46). To a stirred solution of LDA (6.5 mmol,  $-65^{\circ}\text{C}$ ) in THF [prepared by the addition of 0.66 g (6.5 mmol) of diisopropylamine to one equivalent of n-butyllithium] was added a solution of 1,6-diazaphenalene (4, 1.0 g, 5.94 mmol in 60 ml of THF and 6 ml of HMPA) from a dropping funnel at a rapid rate. The deep orange-red solution was stirred for another 10 min at  $-65^{\circ}\text{C}$  followed by the addition of methyl iodide (0.92 g, 6.5 mmol) via a syringe. The reaction mixture was stirred at the same temperature for 10 min and then allowed to come to room temperature without removing the cooling-bath. A few drops of water were added, and the solvent removed under reduced pressure to furnish a dark brown viscous oil. Addition of water (100 ml) gave a yellow precipitate which was filtered from the solution, and was washed several times with water to remove residual HMPA. This material was dried to give a yellow solid, mp  $94-96^{\circ}$  which was further purified by elution through a short column of alumina (eluent, THF). The product 46 was a nicely crystalline yellow solid: mp  $104-105^{\circ}\text{C}$ ; IR (KBr) 1630 (s), 1575 (s), 1342 (s), 825 (m), 740 (s); NMR ( $\text{CDCl}_3$ ),  $\delta$  3.04 (3H, s), 5.64 (1H, d,  $J=7\text{Hz}$ ), 6.11 (1H, dd,  $J_1=J_2=7\text{Hz}$ ), 6.27 (1H, d,  $J=4.5\text{Hz}$ ), 6.48 (1H, d,  $J=7\text{Hz}$ ), 7.11-7.47 (2H, m), 8.23 (1H, d,  $J=4.5\text{Hz}$ ); mass spectrum (CI,  $\text{NH}_3$ ) 183 ( $M^++1$ , 100%).

Anal. Calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_2$ : C, 79.11; H, 5.53; N, 15.37. Found: C, 79.00; H, 5.50; N, 15.30.

1-Benzyl-1,6-diazaphenalene (47). A. To a stirred solution of LDA [4.59 mmol, 50% excess,  $-10^{\circ}\text{C}$ , (ice-salt bath) in THF prepared by the addition of one equivalent of diisopropylamine to one equivalent of n-butyllithium] was added 1,6-diazaphenalene (4, 0.514 g, 3.06 mmol) dissolved in 60 ml THF and 5 ml HMPA. Soon afterward the color of the reaction mixture changed from green-yellow to orange. By the end of the addition (2-3 min), the reaction mixture was brownish orange in color, and was allowed to stir at this temperature for another 10 min. Benzylbromide (0.57 g, 30% excess, 3.33 mmol) was then added to the reaction mixture via a syringe. During the addition, the color of the reaction mixture faded and was gradually replaced by a light green color. The reaction mixture was then stirred for 30 min at  $-10^{\circ}\text{C}$  and then allowed to come to room temperature and stirred for another 30 min. A few drops of water were then added to destroy any excess base. The THF solution was then removed under reduced pressure to give a reddish-brown oil. To this residue, water (100 ml) was added, and the resulting solid was filtered. This green-yellow solid was washed several times with water to remove HMPA. This crude product was purified by column chromatography ( $\text{Al}_2\text{O}_3$ , THF) to provide a greenish-yellow crystalline solid (0.46 g, 58.4% yield), 47: mp  $138-139^{\circ}\text{C}$ . IR (KBr) 3025 (w), 1625 (s), 1590 (s), 1570 (s), 1420 (m), 1340 (s), 820 (m), 740 (m); NMR ( $\text{CDCl}_3$ )  $\delta$  4.47 (2H, s), 5.60 (1H, d,  $J=7\text{Hz}$ ), 6.01 (1H, dd,  $J_1=7\text{Hz}$ ,  $J_2=7\text{Hz}$ ), 6.24 (1H, d,  $J=5\text{Hz}$ ), 6.51 (1H, d,  $J=7\text{Hz}$ ), 6.94-7.34 (7H, m) and 8.21 (1H, d,  $J=5\text{Hz}$ ); mass spectrum (CI,  $\text{NH}_3$ ) 259 ( $M^++1$ , 100%).

Anal. Calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_2$ : C, 83.69; H, 5.46; N, 10.84. Found: C, 83.85; H, 5.35; N, 11.06.

B. In a similar experiment use of n-butyllithium (20% excess) directly in place

of LDA provided an 82.47% yield of the 1-benzyl-1,6-diazaphenalene (47). This reaction was done at  $-65^{\circ}\text{C}$ .

1-Methyl-2,5-dichloro-1,6-diazaphenalene (48). This compound (48) was prepared in 85.94% yield under analogous conditions to that described for 1-methyl-1,6-diazaphenalene (46): mp  $167-168^{\circ}\text{C}$  (yellow solid, acetone) IR (KBr), 3100 (w), 1624 (s), 1585 (s), 1500 (s), 1382 (s), 820 (m), 750 (m); NMR ( $\text{CDCl}_3$ )  $\delta$  3.27 (3H, s), 5.72 (1H, s), 6.10 (1H, s), 6.25 (1H, d,  $J=7\text{Hz}$ ), 7.0-7.42 (2H, m); NMR ( $\text{CF}_3\text{COOH}$ ) 4.05 (3H, s), 6.58 (1H, s), 6.75 (1H, s), 7.22-7.60 (2H, overlapping doublets,  $J=8\text{Hz}$ ), 7.95 (1H, dd,  $J_1=J_2=8\text{Hz}$ ), mass spectrum (CI,  $\text{NH}_3$ ), 250 ( $M^+-1$ , 100%), 252 ( $M^++1$ , 67%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_8\text{Cl}_2\text{N}_2$ : C, 57.39; H, 3.21; N, 11.16; Cl, 28.24. Found: C, 57.17; H, 3.03; N, 11.16; Cl, 27.99.

N-Methyl-7-bromo-1,6-diazaphenalene (50). The title compound (50) was prepared in 74.36% yield in a similar fashion (LDA,  $-65^{\circ}\text{C}$ ) to that described previously for 46: mp  $238-240^{\circ}\text{C}$  (greenish-yellow solid); IR (KBr) 3025 (broad), 1623 (s), 1582 (s), 1493 (m), 1213 (m), 822 (w), 769 (w); NMR ( $\text{CF}_3\text{COOH}$ )  $\delta$  4.99 (3H, s), 6.63-6.70 (2H, unresolved overlapping doublets), 7.21 (1H, d,  $J=9\text{Hz}$ ), 7.70-8.10 (2H, m) 8.22 (1H, d,  $J=9\text{Hz}$ ), mass spectrum CI ( $\text{CH}_4$ ) 261 ( $M^+$ , 100%,  $M^++2$ , 91.7%).

Anal. Calcd. for  $\text{C}_{12}\text{H}_9\text{BrN}_2$ : C, 55.19; H, 3.47; N, 10.73; Found: C, 55.00; H, 3.40; N, 10.75.

N-[4-Phthalimido-3-methyl]-pentyl]amino-1,6-Diazaphenalene 23. To a stirred solution of LDA (2.4 mmol, 20% excess,  $-65^{\circ}\text{C}$ ) in THF [prepared by the addition of 0.24 g (2.4 mmol) of diisopropylamine to one equivalent of  $n\text{-BuLi}$ ] was added a solution of 1,6-diazaphenalene 14 (0.336 g, 2mmol in 30 ml THF and 3 ml HMPA) by a dropping funnel at a rapid rate. The deep orange-red solution which resulted was stirred for 19 min at  $-65^{\circ}\text{C}$ , followed by the addition of 1-iodo-4-phthalimidopentane (0.822 g, 2.4 mmol in 2 ml THF) via a syringe. The reaction mixture was stirred at  $-65^{\circ}$  for 10 min, and then allowed to warm to room temperature. The solvent was removed under reduced pressure to furnish a viscous brown residue. Addition of 25 ml of water did not provide a solid. The entire aqueous reaction mixture was then extracted several times with ether (150 ml). The ether layer was washed over with water to remove any HMPA and was dried over anhydrous sodium sulfate. The solvent was removed to provide practically nothing.

Most of the water was removed from the aqueous layer and the residue was taken up in 25 ml of THF. This mixture was purified by column chromatography ( $\text{Al}_2\text{O}_3$ , eluent-THF). A brown viscous oil (1.18 g) was obtained, the NMR spectrum of which contained the signals for the desired compound contaminated with much A greenish-yellow amorphous solid was obtained when a small amount of  $\text{CH}_2\text{Cl}_2$  was added to the brown residue, wt.=0.513 g (66.97%) mp  $220^{\circ}\text{d}$ ; IR (KBr) 3400 ( $\text{H}_2\text{O}$ ), 3070 (w), 2990 (w), 1635 (s), 1600 (s), 1586 (s), 830 (w), 750 (w); NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.10 (3H, d,  $J=6.8\text{Hz}$ ), 1.60 (4H, m), 3.83 (3H, m,  $\text{N-CH}_2$ , d,  $\text{N-CH}$ ), 5.87 (1H, d,  $J=8\text{Hz}$ ), 6.45 (1H, d,  $J=5\text{Hz}$ ), 6.60 (1H, d,  $J=8\text{Hz}$ ), 6.83-7.73 (7H, m) and 8.10 (1H, d,  $J=5\text{Hz}$ ); CI mass spectrum ( $\text{NH}_3$ ), 384 ( $M^++1$ , 100%).

1-[(4-Aminopentyl)amino]-1,6-diazaphenalene 24. A solution of N-[4-phthalimido-3-methyl]-pentyl]-amino-1,6-diazaphenalene 23 (2.21 g, 5.65 mmol contaminated with HMPA) in ethanol (40 ml) and hydrazine-hydrate (3 ml, 100%) was refluxed for 5 hrs. The reaction mixture was cooled and a white solid (0.56 g) precipitated which was discarded after filtration. Removal of the solvent from the filtrate gave a dark brown-green liquid (3.81 g). This residue was subjected to a high vacuum at  $80^{\circ}\text{C}$  for 8 hrs to remove most of HMPA and ethanol to provide a dark colored residue (1.5 g). This material was purified by column chromatography ( $\text{Al}_2\text{O}_3$  eluent- $\text{CH}_3\text{OH}$ ) to afford the desired compound 0.56 g as a viscous liquid: NMR ( $\text{CDCl}_3$ )  $\delta$  0.98 (3H, d,  $J=6\text{Hz}$ ), 1.00-1.93 (6H, m) 2.72 (1H, m), 3.41 (2H, t,  $J=7\text{Hz}$ ), 5.67 (1H, d,  $J=7.2\text{Hz}$ ), 5.97-6.27 (2H, m), 6.45 (1H, d,  $J=7.2\text{Hz}$ ), 7.04-7.37 (2H, m), 8.12 (1H, d,  $J=4.2\text{Hz}$ ).

CI mass spectrum ( $\text{NH}_3$ ), 254 ( $\text{M}^+ + 1$ , 100%).

The dihydrochloride of **24** was prepared by passing dry hydrogen chloride gas into a solution of the diamine **24** dissolved in dry methanol until no more solid separated. A yellow-brown solid was obtained by filtration, however, this salt was quite hygroscopic.

Reaction of 1-methyl-2,5-dichloro-1,6-diazaphenalene with pyrrolidine. A suspension of 1-methyl-2,5-dichloro-1,6-diazaphenalene (0.125 g, 0.53 mmol) in pyrrolidine (5 ml) was refluxed for 2 h until reaction was found to be complete. All excess pyrrolidine was removed under reduced pressure and the residue passes through a short column of silica gel (10 g). Elution with THF (50 ml) provided pure compound, (0.11 g, 78.57%) which was recrystallized from a mixture of chloroform and skelly B. mp 140-141° (green needles), IR (KBr) 2940 (w), 2892 (m), 2850 (w), 1618 (s), 1585 (s), 1534 (m), 1512 (m), 1400 (s), 1328 (m), 1173 (m), 885 (m), 816 (m), 740 (m). NMR ( $\text{CDCl}_3$ )  $\delta$  1.95 (4H, m), 3.16 (4H, m), 3.33 (3H, s), 5.36 (1H, s), 6.23 (1H, s), 6.40 (1H, d,  $J=7.5\text{Hz}$ ), 7.00-7.60 (2H, m). Mass spectrum ( $\text{M}^+$ ) 286.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{16}\text{N}_3\text{Cl}$ : C, 67.24; H, 5.64; N, 14.70. Found: C, 67.16; H, 5.53; N, 14.58.

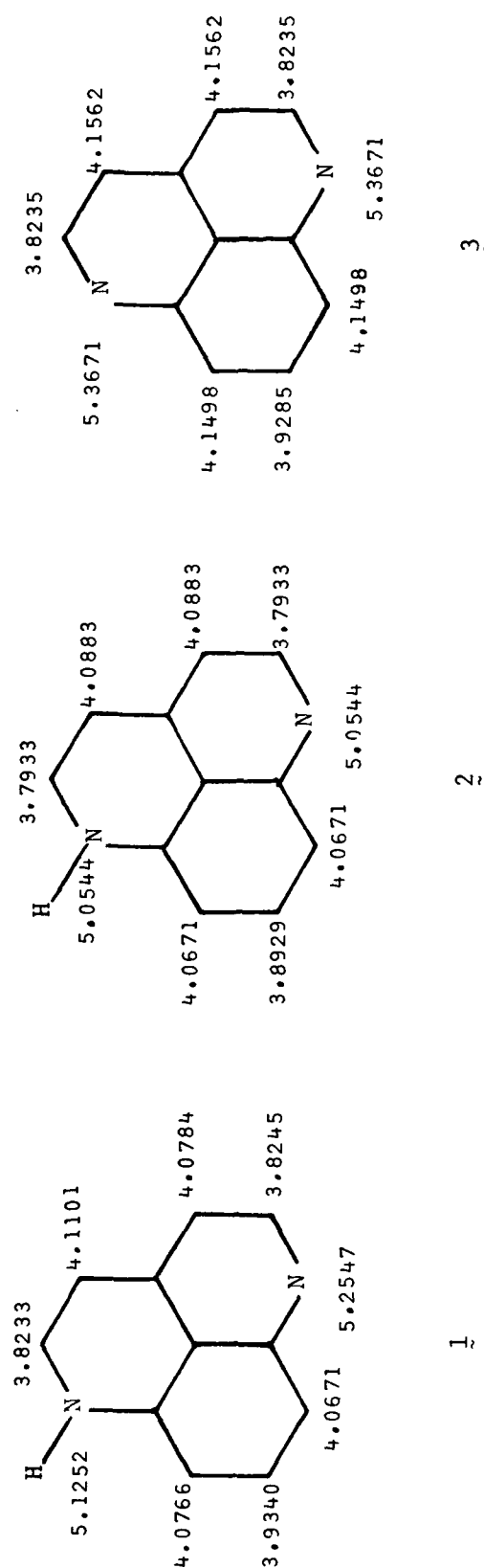


Fig. 1. Total electron densities for 1,6-diazaphenalene 1, the protonated form 2, and the anion 3

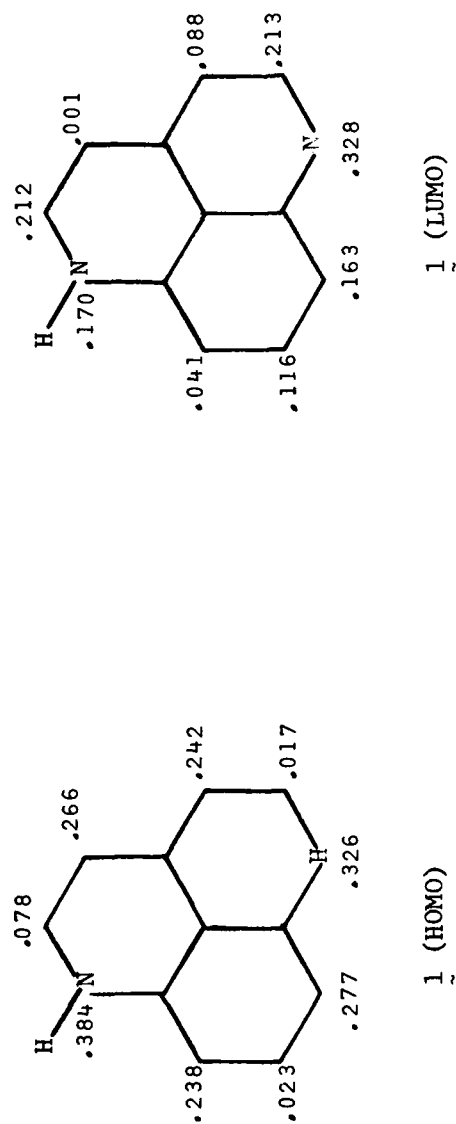


Fig. 2. Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (LUMO) reactions on 1,6-diazaphenylene 1



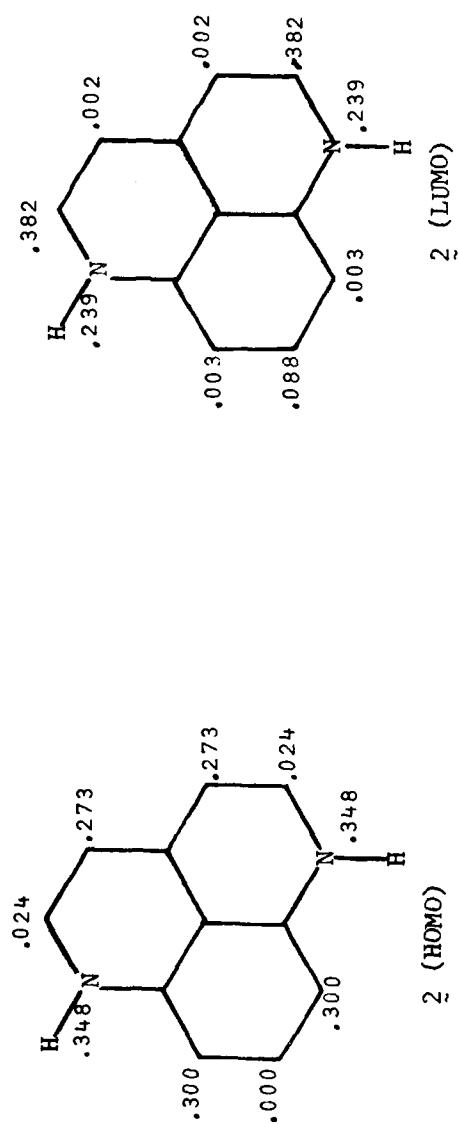


Fig. 3. Calculated HOMO and LUMO densities for protonated 1,6-diazaphenylene 2

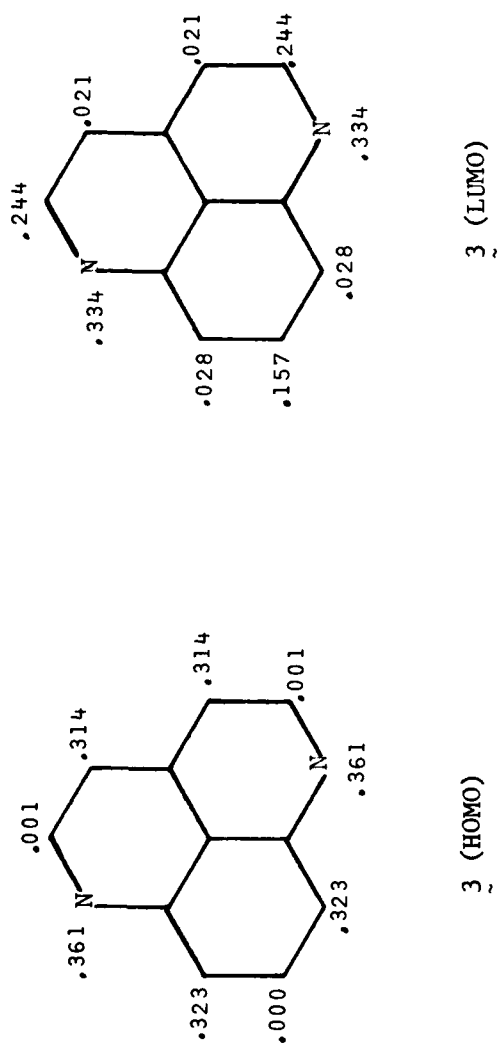


Fig. 4. Calculated HOMO and LUMO densities for the anion 3

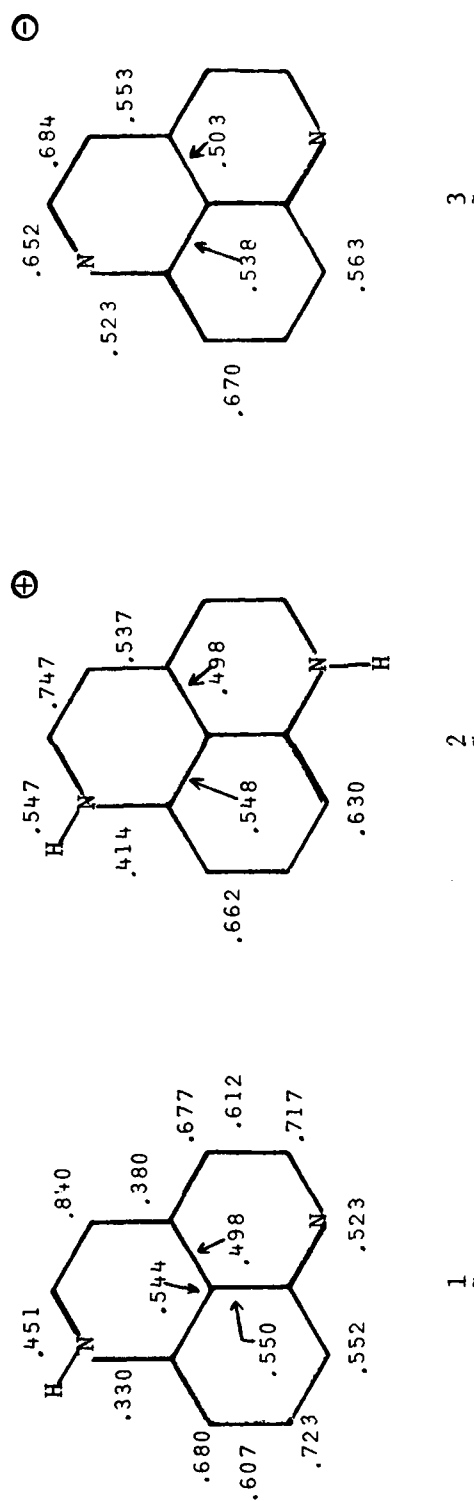


Fig. 5. Calculated bond orders ( $\pi$ ) for 1,6-diazaphenalene **1**, the cation **2**, and anion **3**

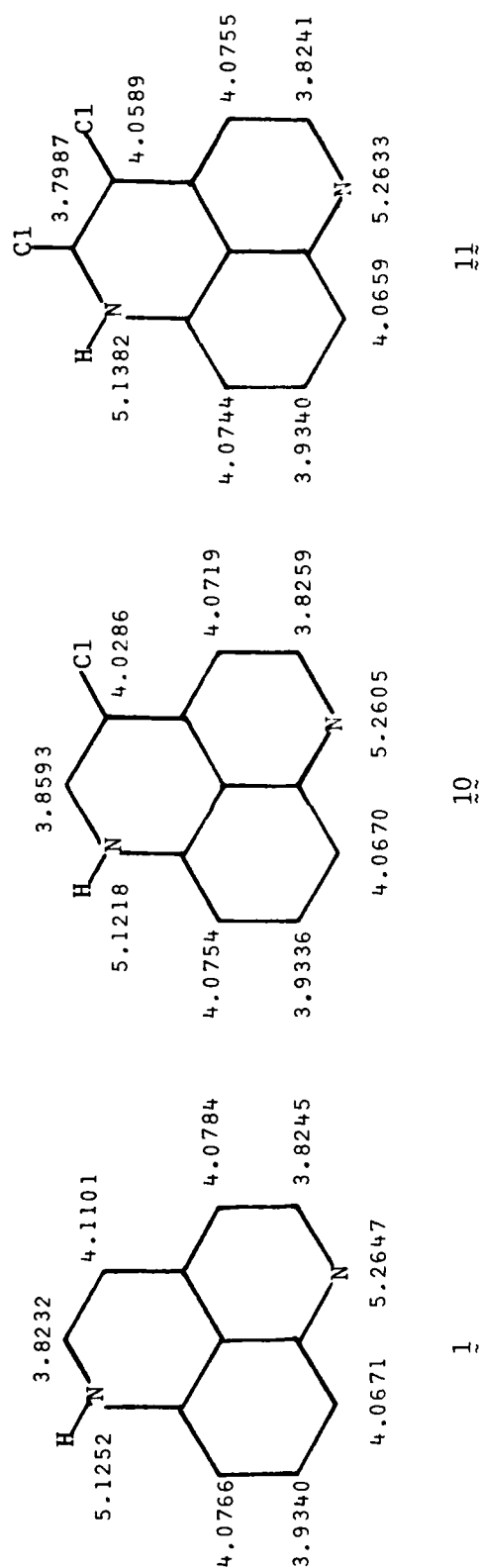


Fig. 6. Total electron densities for 1,6-diazaphenalene 1, 3-chloro-1,6-diazaphenalene 10, and 2,3-dichloro-1,6-diazaphenalene 11

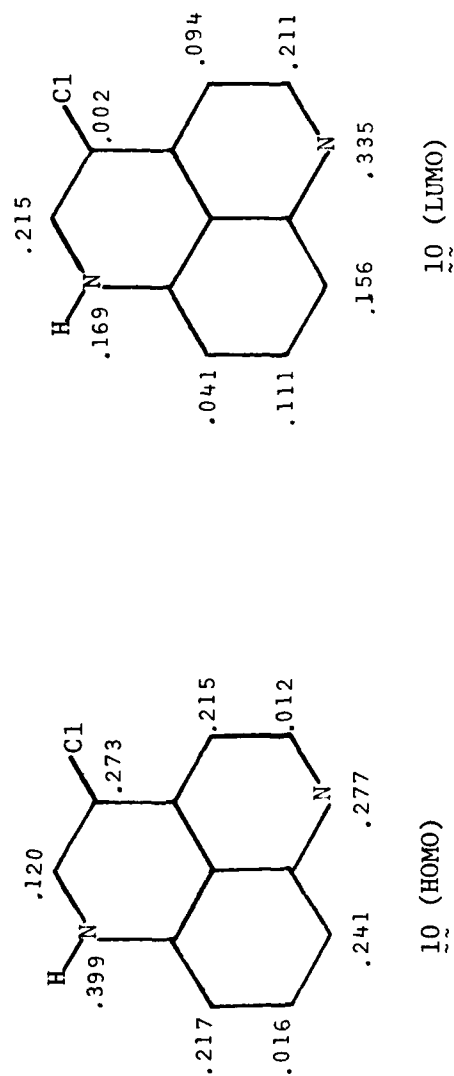


Fig. 7. Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (LUMO) reactions on 3-chloro-1,6-diazaphenalene  $\tilde{\rho}_0$

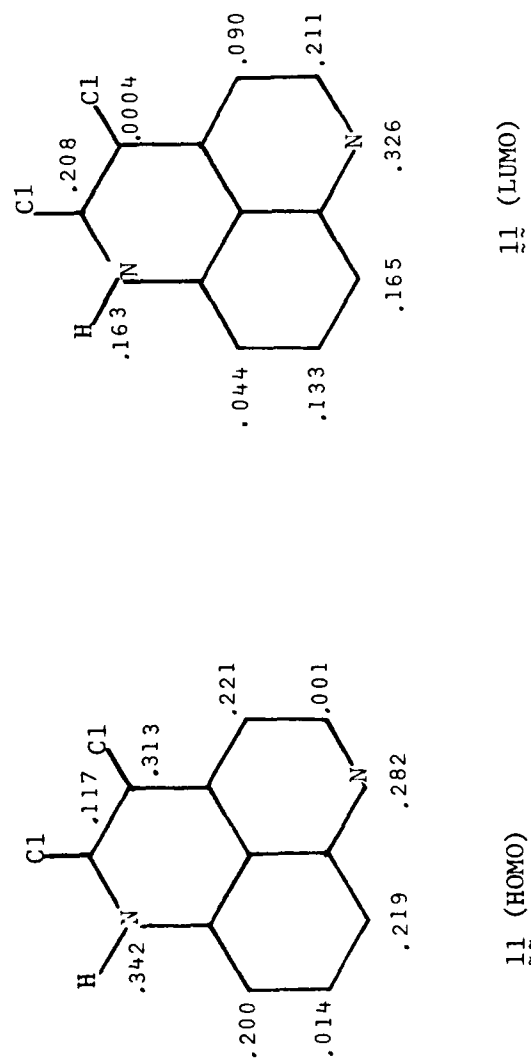


Fig. 8. Calculated densities of frontier electrons for electrophilic (HOMO) and nucleophilic (LUMO) reactions on 2,3-dichloro-1,6-diazaphenalene **11**

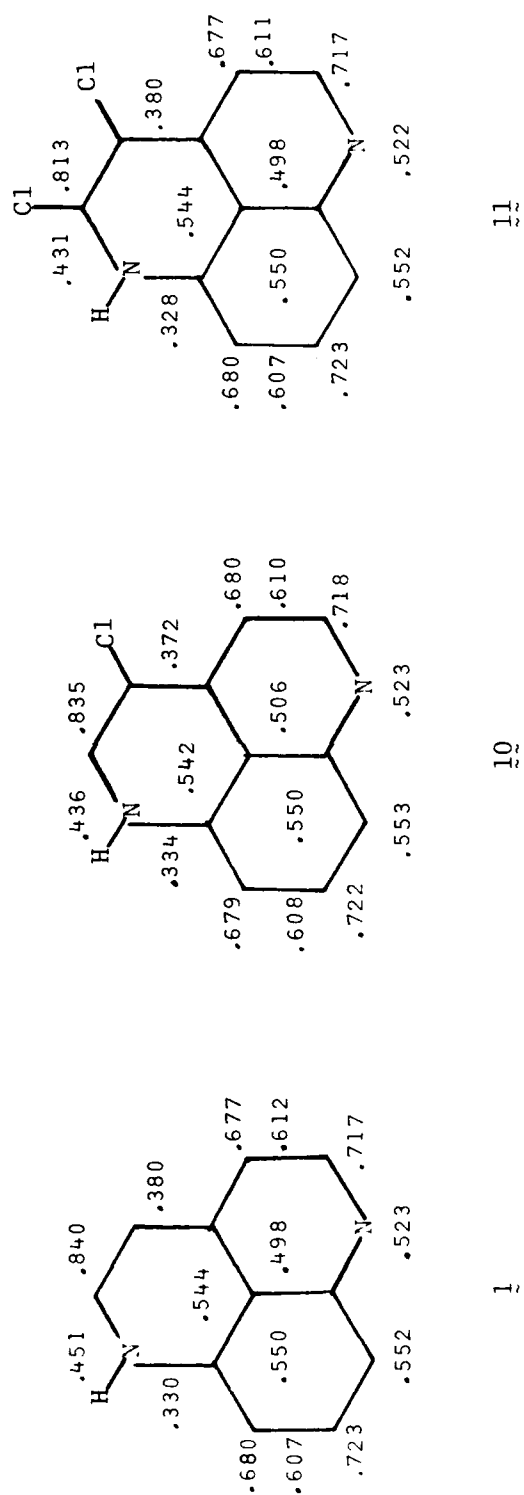
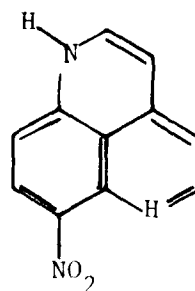
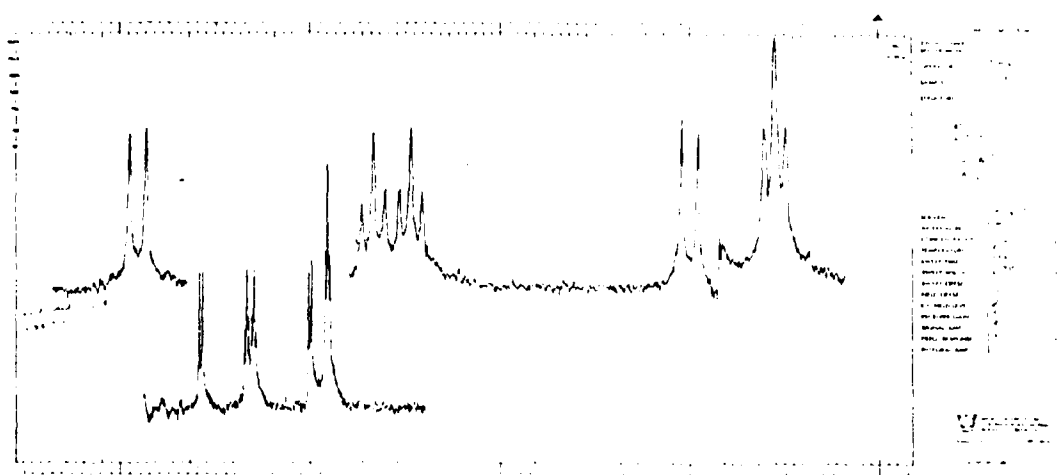
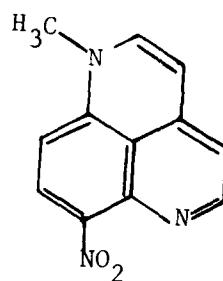
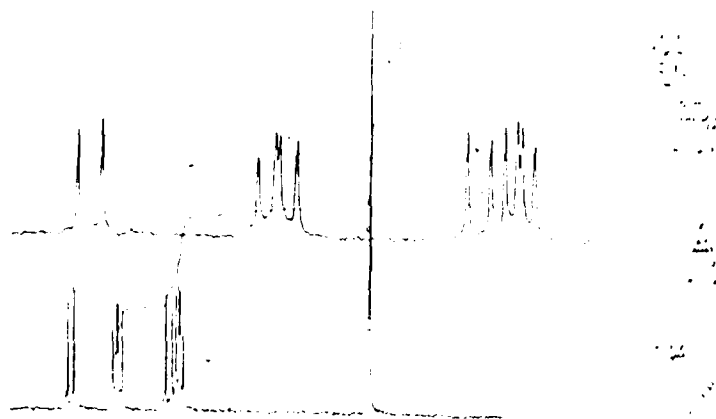


Fig. 9. Calculated bond orders ( $\pi$ ) for 1,6-diazaphenalene **1**, 3-chloro-1,6-diazaphenalene **11**, and 2,3-dichloro-1,6-diazaphenalene **10**

Fig. 10. Proton NMR of 1-Methyl-7-Nitro-1,6-Diazaphenalene and 7-Nitro-1,6-Diazaphenalene, Respectively.





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